Comparison of the Substitution Between Different Tobacco/Nicotine Products as a Function of Tobacco-user Type

Protocol and Statistical Analysis Plan

NCT05177848

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INSTRUCTIONS:

- *Use this "TEMPLATE PROTOCOL (HRP-503)" to prepare a study protocol outlining your research plan.*
- *Depending on the nature of your study, some major sections might not be applicable to your research. If so, simply mark as "N/A." For example, a simple survey might have many sections with "N/A." For subsections (e.g., 1.x or 8.x) you can mark as "N/A"if you are certain that the subsection is not applicable.*
- *Once the IRB/HRPP approves your submission, your latest approved version of the protocol will be stored in the IRB Protocol Management online system.*
- *If your research plan changes and you need to modify the protocol, please submit an amendment to Protocol Management with the requested modifications. Download your current protocol from Protocol Management and indicate the changes/revisions using the track changes feature in order to make review of the modifications easier to follow. If you are unable to use track changes, please create a new paragraph wherever you need to make a change, and indicate "Amendment: Date" before making a change to any section. Protocol management will store the older versions of your protocol if the IRB or HRPP staff need to compare them during the review.*

PROTOCOL TITLE:

Include the full protocol title.

Compare the substitution between different tobacco/nicotine products as a function of tobacco-user type.

PROTOCOL NUMBER:

Include the number assigned in Protocol Management (verify this has been added before submitting protocol to HRPP).

VT IRB # 21-1046

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Is Virginia Tech the primary awardee or the coordinating center of this grant or contract? If not, list the primary institution: Medical University of South Carolina. This Experiment 1 is part of Project 4 of an NIH P01 Grant awarded to

Medical University of South Carolina. Virginia Tech is receiving a subcontract for Project 4. All of the human subject research activities for Project 4, including this first experiment will be carried out at Virginia Tech. Experiment 1 is a single site study.

VERSION NUMBER/DATE:

Include the version number and date of this protocol. Versions should start at 1.0.

Version 1.0 12/03/2021

REVISION HISTORY:

Use this table to keep track of changes. Add more rows as needed.

Revision #	Version Date	Brief Summary of Changes (i.e., the different sections)	Consent Change?
1.0	06/01/2022	Software was updated from Qualtrics to QuestionPro; Session 3 can now be completed in person or remotely; other language was added to clarify the procedures.	Yes
2.0	07/12/2022	Inclusion criteria was changed from "Stable tobacco use patterns for at least three months" to two months.	No
3.0	1/17/2022	Supplementary breath and saliva samples were added; inclusion criterion was updated.	Yes

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1.0 Study Summary

Study Title	Compare the substitution between different tobacco/nicotine products as a function of tobacco-user type.
Study Design	In a within-subject repeated measures design, participants will complete seven ETM conditions, which include five trials assessing different cigarette prices: a) all products at market price (control), b) nicotine vaping products at 1/2 market price, c) nicotine vaping products at 2x market price, d) heated tobacco products at 1/2 market price, e) heated tobacco products at 2x market price, f) nicotine pouches at 1/2 market price, and g) nicotine pouches at 2x market price.
Primary Objective	To compare the effects of different tobacco/nicotine products (i.e., conventional cigarettes, NVPs, HTPs, and NPPs) on tobacco/nicotine purchasing and substitution in the Experimental Tobacco Marketplace, as a function of tobacco user type.
Secondary Objective(s)	N/A
Study Population	Cigarette smokers and dual cigarette/NVP users
Sample Size	N = 52 completers
Research Intervention(s)/ Investigational Agent(s)	A survey consisting of questionnaires and behavioral tasks.
Study Duration for Individual Participants	Session 1: Consent, Assessments and In-laboratory flavor assessment (approximately 2h00). Session 2: Experimental Tobacco Marketplace (approximately 1h30) Session 3: Follow-up (approximately 1h00)
Acronyms and Definitions	NVPs: Nicotine Vaping Products HTPs: Heated Tobacco Products NPPs: Nicotine Pouch Products ETM: Experimental Tobacco Marketplace FBRI: Fralin Biomedical Research Institute VTCRC: Virginia Tech Corporate Research Center

2.0 Objectives

2.1 Describe the purpose, specific aims, or objectives of this study:

Purpose: To compare the effects of different tobacco/nicotine products (i.e., conventional cigarettes, NVPs, HTPs, and NPPs) on tobacco/nicotine

purchasing and substitution in the Experimental Tobacco Marketplace, as a function of tobacco user type.

2.2 State the hypotheses to be tested:

The primary hypotheses are: 1) purchasing of NVPs, HTPs, and NPPs will increase as the price of conventional cigarettes is increased (i.e., they will all serve as substitutes), 2) the effect will be largest when those alternative products are at a reduced price, and 3) dual cigarette/NVP users, because they are multi-tobacco users, will show greater substitution than exclusive cigarette smokers.

3.0 Background

3.1 Summarize the relevant prior research on this topic and gaps in current knowledge within the field of study:

Cigarettes have long been the dominant tobacco product, and the vast majority of the tobacco-related harm comes from their combustion.[1] In recent years, alternative nicotine delivery systems have developed. These products deliver nicotine without combusting tobacco and are marketed as alternative products for addicted smokers.[2] In the previous funding period, we focused on the emergence of NVPs. In this project, we add two additional product classes: HTPs and NPPs.

HTPs (sometimes called Heat Not Burn) are different from NVPs. HTPs heat reconstituted tobacco (tobacco not present within NVPs) at a temperature below the one required for combustion. Because the tobacco is not burned, exposure to harmful chemicals generated by cigarette smoke is substantially lower for HTPs.[3] The prevalence of HTP use in 2020 among current smokers and recent ex-smokers is estimated to be 2.7% in the US. [4] In Tokyo, where it has had the greatest success, IQOS captured 2.4% of the market share for tobacco, with >50% of smokers who tried the product switching entirely from cigarettes.[5] The limited data available on HTPS suggest that they are likely to serve as a substitute for conventional cigarettes.[6]Their role for dual cigarette/NVP users is unknown.

NPPs contain nicotine, but no tobacco,[7] and as a result, may present reduced harm compared to combustible and non-combustible tobacco products, such as smokeless tobacco and snus. A recent pharmacokinetic study showed that the two highest doses of NPP (Zyn) deliver nicotine quickly and at levels similar to traditional smokeless tobacco products.[8] In 2020, the prevalence of NPP use among current smokers and ex-smokers was estimated to be 0.7% in the US. [4] The most recent Nielsen data show that sales from these products are sharply on the rise. However, given that NPPs are oral nicotine products, rather than inhaled products like NVPs and HTPs, whether NPPs would effectively substitute for cigarettes or NVPs among cigarette smokers or dual users is unknown. Further, the strength of substitution for NPPs relative to NVPs and HTPs is unknown. Thus, utilization of NPPs in the ETM may provide data about substitutability that is prescient for understanding the implications of these products for tobacco control.

1. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): : Centers for Disease Control and Prevention (US) 2014. https://www.ncbi.nlm.nih.gov/pubmed/24455788
2. Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction Group. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. Tob Control 2009;18:324–32. doi:10.1136/tc.2008.027318
3. IQOS. https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system (accessed 23 Jun 2020).
4. Li L, Borland R, Cummings KM, et al. Patterns of non-cigarette tobacco and nicotine use among current cigarette smokers and recent quitters: Findings from the 2020 ITC Four Country Smoking and Vaping Survey. Nicotine Tob Res Published Online First: 8 March 2021. doi:10.1093/ntr/ntab040
5. Caputi TL. Industry watch: heat-not-burn tobacco products are about to reach their boiling point. Tob Control 2016;26:609–10. doi:10.1136/tobaccocontrol-2016-053264
6. Adriaens K, Van Gucht D, Baeyens F. IQOSTM vs. e-Cigarette vs. Tobacco Cigarette: A Direct Comparison of Short-Term Effects after Overnight-Abstinence. Int J Environ Res Public Health 2018;15. doi:10.3390/ijerph15122902
7. Robichaud MO, Seidenberg AB, Byron MJ. Tobacco companies introduce 'tobacco-free' nicotine pouches. Tob Control Published Online First: 21 November 2019. doi:10.1136/tobaccocontrol-2019-055321
8. Lunell E, Fagerström K, Hughes J, et al. Pharmacokinetic comparison of a novel non-tobacco-based nicotine pouch (ZYN®) with conventional, tobacco-based Swedish snus and American moist snuff. Nicotine Tob Res Published Online First: 22 April 2020. doi:10.1093/ntr/ntaa068

3.2 Describe any relevant preliminary data:

The Experimental Tobacco Marketplace (ETM) [1], a novel method recently developed, permits estimates of the effects of new policies and products on consumption and substitution in the tobacco marketplace. This methodology places the mix of products, prices, and specific policies under experimental control so as to provide estimates of novel policies obtained under conditions that simulate "real world" circumstances. This approach provides insight into how a given policy may alter consumption, preferences, and substitution among tobacco products. Different policies have been examined with this methodology in adult smokers, as part of the previous funding period. Study 1 examined the impact of e-liquid nicotine strength and showed that the substitutability between cigarettes and NVPs increased as a function of e-liquid strength. The 24mg/mL strength resulted in the greatest substitutability ($p<0.001$; $f=1.05$).[2] Study 2 examined cigarette taxes and e-liquid subsidies. It showed that cigarette taxes decreased cigarette purchases ($p=0.005$; $f=0.45$).[3] Interestingly, e-liquid subsidies had no effects on cigarette purchases, but increased e-liquid purchases ($p=0.013$; $f=0.44$). Study 3 used a hypothetical ETM and replicated the taxes and subsidies conditions from Study 2 among exclusive cigarette smokers and dual cigarette/NVP users in an international context as part of the ITC survey. Analysis of country-specific differences have yet to be explored, however, the US cohort replicates the findings of the lab-based ETM. Note, the effects of

taxes on cigarette purchases observed in Studies 2 and 3 replicate and demonstrate the generality of our findings as related to prior econometric analysis of the impact of national and state taxes.[4] This replication provides an example of reverse translational research demonstrating that the ETM can reflect effects observed in larger populations.[5] Study 4 investigated the effects of NVP use in smoke-free environments on product choice. The results suggest that permitting NVP use in the workplace increased e-liquid purchase on average ($p<0.001$; $f=0.56$), but nicotine concentration had no effect on e-liquid demand intensity. Cigarette demand was unaltered across conditions.[6] This study suggests that allowing NVP use in the workplace may increase the demand for e-liquid without affecting purchases of conventional cigarettes. Collectively, and importantly for the proposed study, our ETM work shows that the substitution between products is dependent upon several factors (nicotine strength, price of the substitutable product, and the type and number of products in the marketplace). In these studies, we change the price as an expeditious, effective, and quantifiable method to promote change. With that change, we can ascertain the likelihood that smokers will defend their consumption or substitute it for another product. In doing so, we can estimate the consequences of a policy constraint before implementation.

1. Bickel WK, Pope DA, Kaplan BA, et al. Electronic cigarette substitution in the experimental tobacco marketplace: A review. Prev Med 2018;117:98–106. doi:10.1016/j.ypmed.2018.04.026
2. Pope DA, Poe L, Stein JS, et al. Experimental tobacco marketplace: substitutability of e-cigarette liquid for cigarettes as a function of nicotine strength. Tob Control Published Online First: 18 April 2018. doi:10.1136/tobaccocontrol-2017-054024
3. Pope DA, Poe L, Stein JS, et al. The Experimental Tobacco Marketplace: Demand and Substitutability as a Function of Cigarette Taxes and E-Liquid Subsidies. Nicotine Tob Res under review.
4. Chaloupka FJ, Grossman M, Bickel WK, et al. The Economic Analysis of Substance Use and Abuse: An Integration of Econometric and Behavioral Economic Research. Published Online First: 1 January 1999.https://www.nber.org/books/chal99-1.pdf (accessed 7 Aug 2020).
5. Shakhnovich V. It's Time to Reverse our Thinking: The Reverse Translation Research Paradigm. Clin Transl Sci 2018;11:98–9. doi:10.1111/cts.12538
6. Freitas Lemos R, Stein JS, Pope DA, Brown J, Feinstein M, Stamborski KM, Tegge AN, Heckman BW, Bickel WK. E-liquid Purchase as a Function of Workplace Restriction in the Experimental Tobacco Marketplace. Exp Clin Psychopharmacol; Advance online publication. https://doi.org/10.1037/pha0000444

3.3 Based on the existing literature, provide the scientific or scholarly rationale for and significance of your research and how will it add to existing knowledge:

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An important aim of tobacco control is to reduce demand for the most harmful products. No study to date has experimentally compared the effects of conventional cigarettes, NVPs, HTPs, and NPPs on tobacco/nicotine purchasing and substitution. A priori knowledge of substitutability across novel and widely used tobacco products may forecast the impact of policies on product switching.

4.0 Study Endpoints

*4.1 Describe the primary and secondary **study** endpoints. See links below for discussion of study endpoints and how they may differ from study objectives. These are most common in clinical trials but are sometimes applicable to other types of biomedical research, as well as social, behavioral, or educational research. See link below for a discussion.*

https://docs.google.com/document/d/1Wocz7K7a0hCQJPPO_khh5l1SQOjhGDDGHzcOPRHR5Tw/edit?usp=sharing

Substitutability: cigarettes, NVPs, HTPs, and NPPs will be compared to assess substitutability as a function of tobacco user type.

*4.2 Describe any primary or secondary **safety** endpoints. These should be included for all studies that are greater than minimal risk. (Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*:

This study will recruit adults who regularly smoke cigarettes and who regularly smoke cigarettes and use NVPs. This study's procedures are not designed to increase daily nicotine use and we do not anticipate any increased risk to participants directly from this study, although there are risks of nicotine use and these are included in the risk section of this protocol and consent.

5.0 Study Design and Statistical Analysis Plan

5.1 Describe the basic study design/approach (e.g., qualitative study using five focus groups of first year students to describe assimilation into the university community; randomized controlled trial of a behavioral change intervention to increase dietary intake of whole grains; pre- post-test evaluation of new pedagogical techniques to improve adult literacy):

In a within-subject repeated measures design, participants will complete seven ETM conditions, which include five trials assessing different cigarette prices: a) all products at market price (control), b) nicotine vaping products at 1/2 market price, c) nicotine vaping

products at 2x market price, d) heated tobacco products at 1/2 market price, e) heated tobacco products at 2x market price, f) nicotine pouches at 1/2 market price, g) nicotine pouches at 2x market price.

5.2 Describe corresponding data analysis plan/approach (e.g., content analysis of focus group transcripts; descriptive analysis followed by linear regression modeling; nonparametric analysis of pre- and post-test measures):

A within-between subject analysis of variance (ANOVA) will test for differences in substitution and demand measures between user types (exclusive cigarette smokers and dual cigarette/NVP users) and relative price scenario (e.g., ½ market price for HTPs). We will test for the interaction between the relative price scenarios and each user type, suggesting a difference in how each user type responds to price scenarios. Order effects will be included in all models to account for the balanced Latin square design for counterbalancing the ETM conditions within the session. We will perform post-hoc contrasts to compare user types, based on our hypotheses.

Additional analyses might be conducted.

6.0 Setting

6.1 Describe the sites or locations where your research team will conduct the research. Consider each of the items listed below:

- *Identify where your research team will identify and recruit potential subjects.*
- *Identify where the team will perform the research procedures.*
- *Describe the composition and involvement of any community advisory board(s).*
- *For research conducted in other locations, describe:*
  - *Site-specific regulations or customs affecting the research at those locations.*
  - *Local scientific and ethical review structure at those locations. Examples include work in other cultures or ethnic groups (within or outside of the U.S.) and work with churches. The HRPP will provide additional guidance for international research.*

Location of Recruitment:

Participants will be recruited from the Roanoke-Blacksburg community via flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). To the extent possible, we will attempt to minimize obstacles to participation. For example,

travel barriers will be addressed by providing transportation or parking costs to participants, and scheduling barriers will be minimized by offering a flexible session schedule.

Location of study:
All methods and measures will be conducted using standard operating procedures at the Fralin Biomedical Research Institute (FBRI) at VTC, the Virginia Tech Corporate Research Center (VTCRC) or a designated site. All staff (including recruitment staff) will have completed human subjects' protection and research training. We have a history of successful recruitment of cigarette smokers and NVP users. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation.

7.0 Study Intervention(s)/Investigational Agent(s)

7.1 Describe the study interventions (including behavioral interventions) and/or investigational agents (e.g., drugs or devices) to be used in this study. Consider each of the items listed below:

- *Drug/Device Handling: If the research involves drugs or devices, describe your plans to store, handle, and administer the drugs or devices so that they will be used only on subjects, and only by authorized investigators.*
- *Describe whether any of the following will be used: microwaves, X-rays, DEXA scans, general anesthesia, or sedation*
- *If control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference the SOP in this section.*

This study does not involve any smoking cessation interventions. This study does involve experimental manipulation of tobacco/nicotine product price to understand consumer's behavior. Participants will be provided with a FDA approved NVP and HTP to use during the study.

7.2 List the name of all drugs (including any vitamins, supplements, herbs, or nicotine) to be used in the study. Indicate whether they have FDA approval, and list any limitations for their use:

The range of products available to sample and purchase includes: cigarettes, chewing tobacco, HTPs, nicotine gum, nicotine lozenges, nicotine patches, NPPs, NVPs, and snus. All the products that will be available to sample and purchase are FDA approved and available in the real world. Note that as of November 29, 2021, IQOS Devices and Heatsticks were removed from all stores, due to an order issued by the International Trade Commission regarding an ongoing patent dispute. These products are no longer

available for sale in the U.S. However, the ITC order does not impact products that researchers/consumers already have in their inventory.

7.3 List all devices, how they will be used, their purpose in the study, and if they will be used in a manner consistent with their approved uses. If they will be used in ways that are not yet FDA approved, indicate whether they need an IDE or a determination that they are exempt from the IDE Determination. If a determination of significant risk or non-significant risk is needed for any of the devices, include the researcher's recommendation for each of those devices:

Participants will be provided with a NVP and a HTP and instructed how to use according to the manufacturer specifications. Both products are FDA approved.

7.4 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- *Identify the holder of the IND/IDE/abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

N/A

8.0 Procedures Involved

8.1 Describe and explain the study design:

In a within-subject repeated measures design, participants will complete questionnaires on a computer, sample a range of tobacco products, and complete ETM conditions. Specifically, participants will purchase tobacco products in an online store under seven

ETM conditions, which include five trials assessing different cigarette prices: a) all products at market price (control), b) nicotine vaping products at 1/2 market price, c) nicotine vaping products at 2x market price, d) heated tobacco products at 1/2 market price, e) heated tobacco products at 2x market price, f) nicotine pouches at 1/2 market price, g) nicotine pouches at 2x market price.

8.2 Provide a description of:

- *All research procedures being performed*
- *If the study has more than one procedure, session, and/or subject population, describe each procedure, session, and/or study population separately. For complex studies, you are encouraged to include a figure or chart.*

Participants will complete a 1) informed consent, assessment session, and an in-laboratory flavor assessment, 2) an ETM session, and a 3) follow-up session. Session 1 and 2 will be separated by an at home sampling phase and Session 2 and 3 will be separated by an at home product use phase.

1) In the consent and initial assessment session, participants will go through standard consent procedures and then provide a breath to confirm recent levels of smoking. Participants will complete a timeline follow back (TLFB) to assess previous month recent smoking, and consumption of nicotine products, and to determine ETM budget. A survey will administer demographics questions and nicotine/tobacco-related assessments (Questionnaire on Smoking Urges-Brief, Heaviness of Smoking Index, Perceived Health Risk, Product Evaluation Scale, Intention to transition and/or quit, Tobacco awareness and Hypothetical Purchase Task for a range of products). At the end of the session, participants will experience a trial of the ETM that will be used in the next session. For the NVP, HTP and NPP flavor assessment, participants will rank order flavors from a list of available flavors and choose two flavors to try. During the in-laboratory flavor assessment, participants will be provided single-user/individual NVP and HTP devices. A research assistant will read through the manufacturer instructions on how to use the products with the participant. Sampling will occur in our negative air pressure ventilated smoking laboratory, specifically designed for these types of studies. The smoking laboratory is a custom-built laboratory space in ARRC, which was approved as part of the opening of the Virginia Tech Carilion Institute. This laboratory is enclosed to minimize harm to other participants and laboratory personnel. Participants may use the devices throughout the study and won't be asked to return them.

If needed, the informed consent and initial assessment session and flavor assessment can be in different days.

For the sampling phase, participants will be provided with the most preferred flavor of NVP, HTP and NPP to sample during the sampling period. Participants may also be provided with a sample of any other commercially available tobacco product they wish to examine and try.

2) In the ETM session, participants will buy tobacco products to use throughout the next 5 days. Participants will complete a total of 35 purchasing trials each for 5 days' worth of products. They will be exposed to 7 conditions with cigarettes increasing in price. A balanced Latin square design will be used to present the following conditions: a) all products at market price (control), b) nicotine vaping products at 1/2 market price, c) nicotine vaping products at 2x market price, d) heated tobacco products at 1/2 market price, e) heated tobacco products at 2x market price, f) nicotine pouches at 1/2 market price, g) nicotine pouches at 2x market price. Additionally, participants will complete the Questionnaire on Smoking Urges-Brief.

For the five days following the ETM session, participants will be asked not to use or purchase any outside tobacco/nicotine products and not to sell or give away any of their purchases.

3) In the follow-up session, participants will complete a timeline follow back to assess previous week recent smoking, and consumption of nicotine products. A survey will administer nicotine/tobacco-related assessments (Perceived Health Risk, Product Evaluation Scale, and Hypothetical Purchase Task for a range of products). Session 3 will be in laboratory unless participants are having difficulty returning to the lab. If participants are unable to complete the study in person, a Zoom session will be scheduled and participants will interact with study personnel to complete the session. The same computerized assessments will be administered in person and using Zoom.

In all three sessions, participants may be asked to provide breath and saliva to test for recent nicotine/tobacco use. The intent is to compare the two methods of detecting current tobacco and nicotine use. Participants who are available to complete the third session in-lab will be considered for this procedure. Approximately the next six exclusive smokers will be invited to complete this procedure, which will help inform the most appropriate methods for future research.
To collect breath sample, we will use the Icoquit, which is a single-user commercially available device. To collect saliva, we will use the iScreen Saliva Nicotine Test, which is a single-use test also commercially available. Procedures will be conducted following the manufacturers' instructions.
Additionally, participants will complete a TLFB to describe the quantities and times of tobacco and nicotine use in the past 24 hours.

8.3 Describe:

- *Procedures or safeguards intended to <u>reduce the probability and magnitude of risks</u>. (For example: Reducing the risk of injury in a virtual reality study either by having the subjects sit during the study or by providing an obstacle-free space for walking.)*

- *Be sure to describe all drugs and devices used in the research, when they will be administered or used, and their purpose.*
- *Methods used to collect data about subjects. Please upload all data collection forms to Protocol Management. Some common examples are:*
  - *Screening questionnaires*
  - *Survey(s), including online surveys*
  - *Demographic questionnaire(s)*
  - *Interview guide(s), e.g., questions or pool of questions for semi-structured interviews*
  - *Focus group guide(s)*
  - *Other documents used to collect data*

Participation in this study is completely voluntary and participants may choose not to participate at any time.
Participants will be given an FDA approved NVP and HTP to sample/use during the course of this study. Research personnel will provide detailed instructions and demonstration to assure proper use according to the manufacturer specifications.

Information and data from participants will be collected from research staff and from self-reported surveys. Examples of the assessments described in section 8.2 are attached.

8.4 What data will you collect during the study and how you will obtain them? Please include descriptions of electronic data collection, database matching, and app-based data collection:

All of the survey and questionnaire data will be collected using QuestionPro, an online survey platform used to develop, administer, and collect participant data in a secure password protected database.
ETM data will be collected using an experimental online store custom-built by a programmer and used in previous studies.
All tasks will be performed on a computer. Only study personnel will have access to the collected data.

8.5 Who will transcribe or code audio and/or video recordings?:

N/A

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8.6 Include a description of any deception to be used in the study. Include justification for the use of deception (why the deception is necessary), describe the debriefing process, and describe how the study meets all the following criteria for alteration of consent (deception is considered an alteration of informed consent):

- *The research involves no more than minimal risk to the subjects*
- *The alteration will not adversely affect the rights and welfare of the subjects*
- *The research could not practicably be carried out without the alteration/deception*
- *(Optional but encouraged in most cases) Subjects will be provided with additional pertinent information after participation (i.e., debriefing for studies involving deception)*

N/A

8.7 If the study involves long-term follow-up (once all research related procedures are complete), describe what data will be collected during the follow up period and when it will occur:

N/A

9.0 Data and Specimen Long Term Storage and Use

9.1 If you will store data or specimens for future use, describe where you will store the data or specimens, how long they will be stored, and how and by whom the data or specimens will be accessed:

All participant data, including electronic data, will be stored in secure places to protect confidential participant information. Secured places will include locked filing cabinets, locked rooms accessible only to study personnel, and/or password-protected databases. Moreover, all data will be quality controlled in preparation for data analyses. All discrepancies in data entry will be checked against the raw data source, and the correct data entry will be used. All data entered into spreadsheets and databases will be coded by participant ID number and not by name (i.e., first and last name). Additionally, all entered data will be backed up on secure password-protected servers. Computers used in the studies will also be password protected, accessible only by study personnel. IRB regulations will be strictly adhered to in the conduct of the proposed research.

Specifically, prior to implementation of any protocol changes, amendments will be submitted to the IRB for approval.

9.2 For specimens, list the data to be stored or associated with each specimen:

N/A

9.3 Describe the procedures to release data or specimens outside of the research team, including the process to request a release, approvals required for release, who can obtain data or specimens, and what data will be provided with specimens:

Investigators will adhere to all NIH requirements regarding data sharing. Participant data collected in this project will be de-identified before sharing for analysis outside of the study team. As part of this process, all investigators will be required to agree to the following conditions: 1) will adhere to the reporting responsibilities; 2) will not redistribute the data beyond the requesting individual and named collaborators; 3) will give appropriate acknowledgement; 4) will not use the data for commercial purposes; and 5) will obtain appropriate ethical approvals.

Results from research conducted will be shared and disseminated, including: regular project meetings, annual meetings, symposia, workshops, and/or conferences for related groups. Manuscripts will be written and submitted for publication in peer-reviewed journals/conferences, following the NIH Public Access Policy guidelines. All necessary ethical approvals will be obtained.

Data requests will be reviewed by the principal investigator and data will be shared with the expectation of acknowledgment of funding source and primary study team.

9.4 Describe the identifiers to be included with stored data or specimens, as well as any key or code that could be used to make them identifiable. Describe where the code will be stored, who will have access to it, and when it will be destroyed:

Original signed consent forms will be stored in a study specific binder for this protocol, separate from all other study documents, identifying information, and data collection.

All screened participants are assigned study IDs that are thereafter associated with all collected data, whether paper or electronic. The electronic de-identified data is stored on

the shared servers which are password protected. Non-electronic data that is collected is stored in study-specific binders identified only by study ID. These binders are stored in a locked room within ARRC.

Study ID and full name are available together electronically only in REDCap [1], a widely used secure web-based application that enables us to build and maintain a participant database. Specifically, we use REDCap to collect demographic and other screening criteria for eligibility for study enrollment. This service is password protected and has been approved by Virginia Tech IRB.

1. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. doi:10.1016/j.jbi.2008.08.010

9.5 Please select the identifiers you will obtain (whether directly from participants or from another source), including but not limited to:

☒	*Name*
☒	*Geographical subdivisions smaller than a state, including street address, city, county, precinct, zip code, and equivalent geocodes (note, the initial three digits of a zip code are not considered identifiable)*
☒	*Elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death, and single year of age over 89 and all elements of dates (including year) indicative of such age (note, such ages and elements may be aggregated into a single category of age 90+)*
☒	*Phone numbers*
☐	*Fax numbers*
☒	*Electronic mail addresses (e-mail)*
☒	*Social Security numbers*
☐	*Medical record numbers*
☐	*Health plan beneficiary numbers*
☐	*Account numbers*
☐	*Certificate/license numbers*
☐	*Vehicle identifiers and serial numbers, including license plate numbers*
☐	*Device identifiers and serial numbers*
☐	*Web Universal Resource Locators (URLs)*
☐	*Internet protocol (IP) address numbers*
☐	*Biometric identifiers, including finger and voice prints (audio recording)*

☐	*Full face photographic images and any comparable images (including video recording)*
☐	*Student record number or identification number*
☐	*User name for online or computer accounts*
☐	*Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)***:** Click here to explain.

10.0 Sharing of Results with Subjects

10.1 Describe whether you will share results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) with subjects or others (e.g., the subject's primary care physician). If so, describe how you will share the results and include this information as part of the consent document. Upload materials you will use to explain the results to subjects:

We will not share study results or individual results directly with the study participants or others.

11.0 Study Timelines

11.1 Describe:

- *The duration of an individual subject's participation in the study (for example, 1 hour, 2-4 weeks, 3-5 years).*
- *The amount of time expected to enroll all study subjects (weeks, months, years, etc.)*
- *The amount of time expected for the investigators to complete this study including primary data analyses.*

1) Participant's schedule

The participation of one subject is expected to take approximately 2 weeks. Session 1 (Consent, Assessments and in-laboratory flavors assessment) is estimated to take approximately 2h. Session 2 (Experimental Tobacco Marketplace) is expected to take approximately 1h30. Session 3 (follow-up) is estimated to take approximately 1h00. *Note that participants will sample/use products between sessions 1 and 3.

2) Study timeline

Enrollment and data collection are expected to take 1 year.

The study team has projected this study to take approximately 1.5 years to complete enrollment, data collection and data analysis.

12.0 Inclusion and Exclusion Criteria

12.1 Describe how you will screen individuals for eligibility. When will screening occur and what procedures will you use? Upload any screening scripts or surveys to Protocol Management:

We currently use a master screening, which occurs prior to enrolling participants into our research protocols, to effectively decrease attrition in our studies by ensuring that participants meet all inclusion/exclusion criteria prior to enrolling into a study.

12.2 Describe the eligibility criteria that define who will be included and who will be excluded from enrollment for each procedure of your study. Include any geographic criteria (e.g., Virginia Tech undergraduate students, a national sample of adults with engineering degrees, minors aged 8-12 in the New River Valley, university faculty in Virginia and Paris, France):

Inclusion criteria:
- Provide informed consent
- Be at least 21 years of age or older
- Provide a breath sample for measuring carbon monoxide (CO ≥ 8 ppm)
- Stable tobacco use patterns for at least two months
- Be willing to sample NVPs, HTPs, and NPPs.

For exclusive cigarette smokers:
- Smoke at least 10 cigarettes daily and do not use NVPs regularly (no more than 9 times in the last month).

For dual cigarette/NVP users
- Smoke at least 10 cigarettes daily and use NVPs for at least 3 times in a week (report use of closed nicotine salt system)

Exclusion criteria:
- Have plans to move out of the area
- Have a serious or unstable physical or mental health condition
- Taking a tobacco cessation medication or medication that interferes with nicotine metabolism, motivation or reinforcement
- Report concrete, immediate plans to alter/quit using their usual nicotine products at the beginning of the study

12.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate them in the description of your subject population.)

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- *Minors, as defined by state law where the study is performed (infants, children, teenagers)*
- *Pregnant women (can be included in minimal risk studies by mentioning in section 13.1)*
- *Prisoners (including all incarcerated individuals)*
- *Adults not capable to consent on their own behalf*

This study will focus on cigarette smokers and dual cigarette/NVP users. We will not include individuals under the age of 21 in compliance with Virginia state law. Minors, pregnant women, prisoners, and adults not capable to consent on their own behalf will be excluded from this study.

13.0 Vulnerable Populations

13.1 If the research involves individuals who are vulnerable to coercion or undue influence, please describe additional safeguards you will include to protect their rights and welfare. Consider the applicable items listed below:

- *If the research involves Virginia Tech students, indicate whether these are students of any of the investigators. If so, describe whether the activities will take place during class time as part of the curriculum and the steps you will take to reduce the possibility that students feel obliged to participate in order to improve their course grade. The HRPP can provide further guidance as needed. Describe whether you will request access to student records (e.g., SAT, GPA, GRE scores).*
- *If the research involves employees of Virginia Tech or the research sponsor, describe steps you will take to ensure that the employees are freely participating and describe how their data will be protected from inspection by their supervisors.*
- *If the research involves Virginia Tech NCAA athletes, you must obtain approval from the athletic department.*
- *For research involving Montgomery County Public Schools, you must obtain county approval (after obtaining contingent Virginia Tech approval). Other locales have different requirements; please check on these and describe here. 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 be uploaded as a supporting document.*
- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information in this protocol.*

- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information in this protocol.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research (minors), review the "CHECKLIST: Minors (HRP-416)" to ensure that you have provided sufficient information in this protocol.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information in this protocol.*

Virginia Tech Students might participate in the study if they meet the inclusion criteria, although students will not be directly recruited because of their status. However, no students that have had or have any relationship with this lab will be included.

14.0 Number of Subjects

14.1 Indicate the total number of subjects to be enrolled and how this number was determined (e.g., sample size calculation [show], number of available subjects in a finite pool, number of tests funding award would allow):

In this study, we require n=52 (N=78 accounting for 33% attrition) participants to complete the study when using repeated measures with two groups and two measurements per participant.
Our sample sizes are based on a repeated-measures within-between interaction ANOVA design using medium effect size (f=0.25) and 80% power. Note the effect sizes observed in preliminary data ranged from f=0.29 to f=1.05. Given that the products used in these experiments are untested (i.e., NPPs and HTPs), we conservatively selected a medium effect size of f=0.25. To account for multiple testing, we will control for five comparisons in each experiment; therefore, we use an alpha of 0.01.

We have been successfully recruiting cigarette smokers and e-cigarette users in our community for the past 10 years. Based on our experience with prior studies, we anticipate that 33% of participants don't complete the study.

14.2 If this is a multi-site study, indicate the number of subjects to be enrolled at this site and the total to be enrolled from all sites:

N/A

14.3 If applicable, indicate the number of potential subjects you expect to screen for enrollment, and the number of subjects you will need to complete the research procedures:

As stated previously, we have developed and are currently using a separate pre-screening protocol, which occurs prior to enrolling participants into our research protocols. As described above, we anticipate enrolling 78 participants to complete a total of 52 participants.

14.4 If the study has more than one procedure, indicate the total number of subjects to undergo each procedure separately:

All participants will undergo all three sessions unless they withdraw consent.

15.0 Recruitment Methods

15.1 Describe when, where, and how you will recruit potential subjects:

Participants will be recruited from the community via flyers, word of mouth, and electronic advertisements (e.g., Craigslist, Facebook). Participants will be contacted if they have given prior permission (through previous informed consent form) or by completion of a confidential pre-screening questionnaire.

15.2 Describe the source of subjects (for example, clinic patients with specific conditions, students in the library, community members at a gathering, or members of a local gym):

Participants will usually be from the Blacksburg-Roanoke and surrounding areas.

15.3 Describe the methods that you will use to identify potential subjects:

Flyers and ads will generally describe the study and direct potential participants to either call our lab to screen over the phone or to complete our online pre-screener. Participants may also pre-screen in person.

15.4 Describe materials that you will be use to recruit subjects. Attach copies of these documents with this protocol in Protocol Management and be sure to include the IRB protocol number on each document.

- *For flyers, attach the final copy of printed flyers.*
- *For Virginia Tech News, Facebook postings and ads, newspaper ads, websites, MTurk/SONA/online survey systems, etc., attach the final wording and graphics to be used.*
- *For email recruitments, please include the subject line.*
- *For advertisements meant for audio broadcast, please submit the wording of the advertisement prior to taping (to avoid having to re-record with approved language) and submit the final recorded version for IRB review before use.*
- *Describe any compensation to subjects. Separate compensation into appropriate categories, such as: reimbursement for expenses, time and effort, and additional incentives for study participation. For each category, specify the amount (including any pro-rated amount), schedule, and method of payment.*

Flyers to be used in community and online posting are attached.

Compensation for this study is for time and effort and an additional incentive for study completion.

1) Time and effort:

Compensation is distributed according to individual progress through sessions. Participants may receive up to $150 for participating in this study, according to the following:

Session 1 (up to $25)
- $10 for completion of the consent
- $10 for completion of the assessment session
- $ 5 for the in-lab flavor assessment

Session 2 (up to $55)
- $25 for product sampling
- $30 for completion of the Experimental Tobacco Marketplace session

Session 3 (up to $70)
- $35 for the follow-up visit
- $35 bonus for completing the study

Participants who are invited to provide supplementary breath and saliva samples will be additionally compensated up to $10 per session.

2) Travel:

In addition to the above compensation for participation, participants may receive additional compensation for travel time, e.g. $11.00 per hour, consistent with Virginia minimum wage. Research personnel may also arrange and pay for cab or public transportation.

To allow for payments that are both convenient and rapidly available, we will 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.

16.0 Withdrawal of Subjects

16.1 Describe circumstances under which you anticipate subjects could be withdrawn from the research without their consent:

Participants could be withdrawn from the study if they exhibit or report unstable medical illness, unmanaged psychiatric or neurological disorder, violation of research center policies or failure to attend scheduled sessions or to complete any of the study procedures. We will also stop participation if their answers or performance suggest that it is not safe and appropriate for them to continue in the study.

16.2 If applicable, describe any procedures for orderly termination (e.g., discontinuation of a study drug or debriefing after a behavioral intervention):

If a participant is withdrawn from the study, they will be informed the reasons for terminating their participation. If a participant is withdrawn or voluntarily discontinues, their compensation for the study will be pro-rated accordingly.

16.3 Describe procedures that you will follow when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection (e.g., participant declines to continue with regular blood draws, but continues with periodic behavioral questionnaires):

If a participant is discontinued, they will be withdrawn from the entire study.

17.0 Risks to Subjects

17.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include for the IRB's consideration a description of the probability, magnitude, duration, and reversibility of the risks. Consider

physical, psychological, social, legal, privacy, and economic risks. Do not indicate "No risk" or "N/A." Instead, for studies with very low risk (e.g., anonymous online questionnaire on a mundane topic) indicate "The investigators are not aware of any risks from participation in this study." or "No more than risks than are found in everyday life." The example consent form presents a tabular method for risk information, which you can also use here. Common risk types include:

- *Physical (e.g., potential for pain, discomfort, infection)*
- *Psychological (e.g., potential for stress, discomfort, and/or embarrassment)*
- *Social (e.g., potential for discrimination or stigmatization and disruption of personal and family relationships)*
- *Legal (e.g., potential for disclosure of illegal activity, negligence)*
- *Privacy (e.g., potential for personal information being accessed, used, or disclosed without the subjects' knowledge or consent, breach of confidentiality/security)*
- *Economic (e.g., potential for individuals to lose access to economic services, employment, insurability)*

There will be no direct costs for participation, although there are risks.

1. Possible embarrassment: This may result from answering questions that participant considers sensitive. Some of our questions will ask for information about medical and psychiatric conditions and/or drug use.

2. Possible discomfort: There is also the possibility that participant may become bored or frustrated during the research sessions.

3. Loss of confidentiality: The research team will employ every effort to maintain participant confidentiality, however the loss of confidentiality is a potential risk.

4. Adverse effects associated with nicotine use: Because the present experiment allows and sometimes involves self-administering nicotine products, participants might experience adverse effects associated with the use of such products (e.g., nausea, vomiting, dizziness, diarrhea, weakness, rapid heartbeat, minor increase in throat or sinus irritation).

5. Adverse effects associated with nicotine withdrawal: participants might experience adverse effects associated with withdrawal from nicotine (e.g., dizziness, headache, irritability, sleepiness, decreased alertness, difficulty concentrating, impatience, sleeplessness, and increased eating).

6. NVP/HTP/NPP exposure: Participants may not enjoy sampling the study products.

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

17.2 Indicate the measures you will use to minimize risks and monitor subjects for safety. (e.g., asking a subject at regular intervals to rate how they are feeling from 1 to 10, or to slowly crouch in order to check their balance.)

Informed Consent. All consenting methods will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with human subjects protection training. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation.

Protections against risk. Participants will be screened, using medical history and structured interviews for a history of medical contraindications (e.g., pregnancy, recent myocardial infarction) and current unstable medical illnesses. Participants will be free to withdraw from the study at any time. 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. Participants will also be told that they can stop using the study products at any time.

The risks enumerated above will be addressed by the following:
1. Possible embarrassment: Participants are free to refuse to answer questions and withdraw from the study at any time.

2. Possible discomfort: Participants will able to selected a date and time of their choice to start the study. They will also be given breaks during sessions, if desired. To increase data validity and reliability, breaks will be incorporated within the ETM session.

3. Loss of confidentiality: The use of ID numbers for participants, and keeping all data in a locked cabinet in locked offices, will protect confidentiality. Password protected computer databases will have coded identifiers. Master databases linking subject names to study ID numbers will be kept separate from the data. These screening, monitoring, and confidentiality procedures have been in effect for decades and for thousands of participants across the various protocols employed by our group across various institutions.

4. Adverse effects associated with nicotine use: Participants will be informed of the potential adverse effects prior to sampling nicotine products.

5. Adverse effects associated with nicotine withdrawal: Participants will be informed of the potential adverse effects of stopping use of nicotine products.

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6. NVP/HTP/NPP: Participants are only required to try, but not to keep using the NVPs, HTPs and NPPs throughout the study, if they don't want to. Participants will be asked about any health changes throughout the study.

17.3 If applicable, indicate which procedures might have risks to the subjects that are currently unforeseeable. This will be rare, and usually applicable when testing a new drug or device or a new use of an existing drug or device:

The use of study product may have risks to participants that are currently unforeseeable. However, see section 17.2 for details on how these risks will be monitored and mitigated.

17.4 If applicable, indicate which procedures might have risks to an embryo or fetus should the subject be or become pregnant:

Nicotine/tobacco use can be a risk to an embryo or fetus. However, during the consent session, female participants will be tested for current pregnancy. Currently pregnant females will be discontinued from participation.

17.5 If applicable, describe risks to others who are not subjects (e.g., collection of sensitive health data that might affect sexual partners if disclosed, mandatory reporting of abuse, DNA testing that might affect family members or relationships):

N/A

18.0 Potential Benefits to Subjects

18.1 Describe the potential benefits that individual subjects might experience from participating in the research. Include the probability, magnitude, and duration of the potential benefits, as this will be useful to the IRB's risk:benefit analysis. Do not include benefits to society or others. Do not list monetary or non-monetary compensation for participation, as this is not a benefit These should be included in section 2 or 3 of this document:

Participants will not directly benefit from participating in this study. However, the current study may help identify effective methods of assessing the use of tobacco products as well as policy changes, which may help the health of people in the future.

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18.2 If applicable, specify that there are no anticipated direct benefits for participants:

There are no anticipated direct benefits for participation in this study.

19.0 Data Management and Confidentiality

19.1 Describe procedures that you will use for quality control to ensure validity of collected data:

The PI will oversee monitoring of the data collection procedures. These procedures will be reviewed regularly in a number of settings. For instance, issues pertaining to data validity and integrity will be addressed formally during regularly scheduled study personnel meetings in which all study personnel, including the PI, will be in attendance. Issues pertaining to participant safety also will be addressed at these meetings.

19.2 Describe any existing data or biospecimens you will obtain as part of this study. Include:

- *Variables or samples to be obtained*
- *Source of the data or specimens*
- *Your authorization to access or receive the data or biospecimens*
- *Whether the data or biospecimens are publicly available*
- *Whether the data or specimens you receive will contain identifiers*

We may collect urine samples to test for pregnancy, breath samples for carbon monoxide and saliva to assess recent levels of smoking. All tests will be used to obtain the desired measurement and then appropriately discarded, i.e., the tests/samples will not be retained.

19.3 Describe the steps that you will take to handle and secure study data during data collection, storage, use, and transmission. Include information about training of study staff, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, separation of identifiers and data, etc.:

N/A

19.4 For multi-site studies, describe how data or specimens will be handled and secured for each site (e.g., central or disseminated data storage, data coordinating center):

N/A

19.5 Describe the plan for data disposition following the conclusion of the study (e.g., long term maintenance of data, data destruction methods).

- *What information will be included in the long term storage of data or specimens?*
- *How long will the data or specimens be stored?*
- *Where and how data or specimens will be stored?*
- *Who will have access to the data or specimens during long term storage?*
- *Who is responsible for receipt or transmission of the data or specimens?*
- *How will data or specimens be shared or transported?*
- *When and how will personal identifiers be destroyed?*

All behavioral data collected in this study (including participants' characteristics, tobacco related assessments and tobacco purchasing) 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. To secure study data computer databases will have coded identifiers, only ID numbers will be used, data will be kept in secure locations and/or in locked offices. Access to study data will be limited to study personnel who have completed the IRB Human Subjects Training and who have been delegated the responsibility of data collection, management, or analyses by the PI. Currently, there are not plans for data to be sent/transmitted outside the research group. In the event that someone requests the data, only de-identified data will be shared by the lead and principal investigator though a secure virtual server. Personnel identifiers may be kept long term if participants express interest in being considered for future research.

20.0 Provisions to Protect the Privacy Interests of Subjects

20.1 Describe the steps that you will take to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on with whom they interact or to whom they provide personal information (e.g., collecting the minimal amount of private information required to complete the study, protecting the data once it is obtained):

The amount of private information collected in this study is minimal. The information collected is necessary to assure subject safety, completion of the study and proper compensation. Procedures to keep the information safe are described in section 9.4.

20.2 Describe steps that you will take to make subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures (e.g., use of a same gender investigator to place sensors on the torso, a private changing area if clothing must be changed, sensitivity when discussing pregnancy testing with subjects, making it clear on surveys that participants can discontinue at any time, not asking questions about private or sensitive issues unless necessary for the research):

The locations where this study will be conducted have private offices, individualized computer testing and interview rooms. In cases in which private information is collected, the participant is in a private interview room with a trained research staff member. The lab is equipped with white-noise machines to reduce excess noise and maintain confidentiality. All participants are informed that their information is confidential.

20.3 Describe how you plan to access existing sources of information about the subjects (e.g., medical records, grades) and how you will protect participant privacy through the data security plan:

Participants who have previously given consent to be contacted for future studies will be searchable in the REDCap database. Eligibility criteria, based on demographics and current nicotine/tobacco use, may be reviewed to contact potentially eligible participants for this study.

20.4 Describe any required reporting that might occur as a result of your research questions, study populations, and data collection methods. Examples for Virginia and Virginia Tech include:

- ***Any*** *suspicions (e.g., circumstantial, disclosed) of child abuse (physical, emotional, sexual) and neglect*
- *Sexual discrimination and/or sexual violence that involves a student*
- *Disclosure or signs of intention to harm oneself (i.e., suicidal ideation and/or plan)*

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- *Disclosure or signs of desire to harm others (i.e., homicidal ideation and/or plan)*
- *Suspected abuse, neglect or exploitation of vulnerable adults (e.g., individuals with a disability, elderly persons)*

We do not expect any required reporting to occur as a result of our research questions and data collection methods. However, as a safeguard, we include in our consent form that any instances of child or elderly abuse or intent to harm self or others will be reported. Any cases of disclosure or signs of sexual discrimination and/or sexual violence will be reported according to Title IX report procedures.

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety monitoring is <u>required</u> when research involves greater than minimal risk and is sometimes appropriate for other studies.

21.1 Describe:

- *The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe (e.g., periodic reporting to the IRB, establishing a data monitoring committee, reporting data monitoring committee findings to the IRB and the sponsor).*
- *What data you will review, including safety data, unexpected events, and data that show the ability to produce the intended results.*
- *How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects).*
- *The frequency of data collection, including when safety data collection starts.*
- *Who will review the safety data and with what frequency.*
- *The statistical tests for analyzing the safety data to determine whether harm is occurring.*
- *Any conditions that will trigger an immediate suspension of the research (e.g., a serious adverse event).*

The study leader and PI will review any reported health changes or adverse events and report as necessary.

22.0 Compensation for Research Related Injury

22.1 If the research involves more than minimal risk to subjects, describe the available compensation in the event of research-related injury, if any:

N/A

22.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury. At Virginia Tech, this is most common for sponsored research:

N/A

23.0 Economic Burden to Subjects

23.1 Describe any costs that subjects might be responsible for because of participation in the research, including any uncompensated costs for items such as transportation, missed work, and childcare:

There are no costs to participate in this study. To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers may be addressed by providing transportation or compensation through additional time.

24.0 Consent Process

24.1 Indicate the process by which you will obtain consent for study participation. Please upload all consent, parental permission, and assent forms, documents, and scripts referenced in this section to Protocol Management.

Describe the following:

- *Where the consent process will take place (e.g., clinic waiting area, classroom, online)*
- *The time interval between sharing the consent information with the prospective subject and obtaining consent. For lab, interview, and focus group studies, the Virginia Tech IRB prefers that subjects have at least 24 hours to review the consent form and study information before the appointment where consent will be obtained. For simple online survey studies, you can typically present the consent information immediately before subjects begin participation.*
- *If applicable, processes to ensure ongoing consent or assent (e.g., for multiple sessions; for research in which a minor will turn 18 during the study; for longitudinal research with minors who will later be asked to provide or affirm their assent).*

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- *Please review "SOP: Informed Consent Process for Research (HRP-090)" for recommended procedure. Describe your process, being sure to include:*
  - *The name and role of all study personnel who will be trained and certified by the PI to conduct the consent process*
  - *The time that will be devoted to the consent discussion*
  - *Steps that you will take to minimize the possibility of coercion or undue influence*
  - *Steps that you will take to gauge or ensure the subjects' understanding*

Participants will be provided with a copy of the consent form following phone or online screening by email or mail when possible. To accommodate "walk-in" study screens and/or participants unable to receive email or physical mail (e.g., without physical address, email address, or access to a computer), we will provide a hard copy of the consent form to review. In all cases, participants will be given as much time as possible to review the consent and ask any questions. Participants will also be informed that they may choose to take the consent with them and return at a later date to enroll into the study. During the consent process, participants will be given adequate time in a quiet room to read (or further review) the written consent form.

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. 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 they understand the conditions of the study, have no more questions, and chooses to participate. Participants unable to provide informed consent for themselves will not be eligible.

Non-English Speaking Subjects

- *Indicate what language(s) other than English are understood by prospective subjects or representatives.*
- *If non-English speakers will be recruited, describe the process you will use to ensure that the oral and/or written consent information provided will be in a language that they understand.*
- *If you translate consent forms and study materials, please provide a certified translation of the form as well as the certification document.*
- *Indicate the spoken language that study personnel obtaining consent will use. Describe how you will assess fluency of personnel obtaining consent to ensure that the translation is accurate.*

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Non-English speakers will not be recruited.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- *Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations (i.e., that it meets the criteria for a waiver or alteration of the consent process).*

N/A

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

- *Describe the criteria that you will use to determine legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted (e.g., in Virginia, individuals under the age of 18 years).*
  - *For research conducted in Virginia, review "SOP: Legally Authorized Representatives, Minors, and Guardians (HRP-013)" to determine which individuals in the state meet the definition of "minor."*
  - *For research conducted outside of the state, please describe the legal requirements for the definition of "minor."*
- *Describe the process for obtaining parental permission.*
  - *Permission from one parent is acceptable for studies that involve no greater than minimal risk OR involve greater than minimal risk but present the prospect of direct benefit to the minor subject.*
  - *Permission from both parents is required in all other cases (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the minor).*
- *Describe whether you will obtain permission from individuals other than parents or Legally Authorized Representatives, and if so, who will be allowed to provide permission. Describe the process you will use to determine these individuals' authority to consent to the minor's general medical care.*
- *Indicate whether you will obtain assent from all, some, or none of the minors. If you will obtain assent from some minors, indicate which minors will be required to assent. Consider chronological age and intellectual capacity when determining who will be required to*

provide assent (e.g., infants are unable to assent. However, teenagers are likely able to read and sign an assent form).

- *When assent of minors is obtained, describe whether and how you will document it. Will minors sign an assent form or give verbal assent?*
- *Attach parental permission and minor assent forms or scripts in Protocol Management.*

N/A

Adults Unable to Consent

- *Describe the process you will use to determine whether an individual adult is capable of consent.*
- *List the individuals from whom you will obtain permission in order of priority (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and non-minor child).*
  - *For research conducted in the Virginia, review "SOP: Legally Authorized Representatives, Minors, and Guardians (HRP-013)" to determine which individuals in the state meet the definition of "legally authorized representative."*
  - *For research conducted outside of Virginia, please describe the legal requirements for obtaining permission from a legally authorized representative in the state where the research will occur.*
- *Describe the process for assent of the subjects.*
  - *Indicate whether you will require assent from all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not.*
  - *If you will not obtain assent from some or all subjects, please provide justification for not obtaining assent.*
  - *Describe whether and how you will document assent.*

N/A

25.0 Process to Document Consent in Writing

25.1 Consult "SOP: Written Documentation of Consent (HRP-091)" for recommended procedures, and describe whether and how consent of the subject will be documented in writing:

Written consent will include participants' printed name, signature, and date from each of the person obtaining consent (e.g., research coordinator/study staff member), and the research participant on the last page. In addition, a copy of the consent form (paper or electronic) will be offered to the study participant.

25.2 If the research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, you can request that the IRB waive the requirement to obtain written documentation of consent (e.g., consent to participate is indicated by pressing a button for an online questionnaire – after the consent information is presented and before the questionnaire begins):

N/A

25.3 If you will document consent in writing, attach a consent document with places for signatures. If you will obtain consent, but not document consent in writing, please attach the consent script or text. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You should use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script:

Written informed consent and consent statement are attached.

26.0 Resources Available

26.1 Describe the resources available to conduct the research. For example, as appropriate:

- *Describe the PI's availability to supervise the research.*
- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*
- *Describe the time that you will devote to conducting and completing the research.*
- *Describe your facilities.*

- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated or unanticipated consequence of participation in the research.*
- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions (e.g., training plans, detailed study notebooks).*

The organizational structure of the study team involves overall leadership by Dr. Warren Bickel, who will assume full responsibility for all aspects of the project, including design and participant eligibility. Dr. Bickel will oversee recruitment and retention of participants. He will also oversee and delegate to the Co-Investigators and other study team members the responsibility of training study personnel, consenting of participants, and data collection. The Research Coordinator(s) and Research Assistant(s) will be trained and supervised as appropriate for any delegated study procedures. Behavioral data analysis will be overseen by Dr. Bickel and conducted by the Co-Is and the Statistician.

All staff involved in the conduct and/or monitoring of this study will have completed the IRB Human Subject Protection Training and Good Clinical Practice Training. Documentation of training will be maintained. The PI will be responsible for continuous data and safety monitoring of all participants enrolled in this study. In terms of standard operating procedures, trained research staff members will administer all assessments.

Participants will be recruited from the community via flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers will be addressed by providing transportation to participants, and scheduling barriers will be minimized by offering a flexible session schedule. All methods and measures will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with human subjects' research training. We have a history of successful recruitment of smokers and drug users. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation. Note that we have been successfully recruiting cigarette smokers and e-cigarette users in our community for the past 10 years and the demographics of participants have been stable.

As far as facilities, the Addiction Recovery Research Center (ARRC; Director, Bickel) is part of the FBRI, located in Roanoke, Virginia. Multidisciplinary research projects include examining the effects of behavioral, pharmacological, and transcranial magnetic stimulation (TMS) interventions as potential therapies for alcohol, cocaine, and nicotine dependence as well as other health behaviors such as obesity. ARRC also develops potential computerized therapies, applies principles from behavioral and neuro-economics to the understanding of addiction, and assesses nicotine product abuse liability.
ARRC resides on the 3rd floor of the FBRI and consists of several laboratories for clinical research. ARRC has private offices, individualized computer testing and

interview rooms. The lab has a ventilated, negative air pressure smoking laboratory that is equipped with computers and five additional behavioral booths, a dedicated TMS suite, and a conference room. The research space also includes an adjacent male and female restroom with one-way observation windows and connecting stainless steel specimen pass-through cabinets. Office space for PI Bickel, Co-Investigators, Project Coordinators, Postdoctoral Associates, and Research Coordinators/Assistants is provided in the FBRI. The ARRC office suite has a copy machine, fax machine, network printer, scanner, and storage space for participant files and supplies as well as comfortable waiting rooms with entertainment (e.g., magazines, television, etc.) for research participants.

VTCRC has a conference room, private offices, individualized computer testing and interview rooms plus a network printer and access to secured shared servers.

27.0 Multi-Site Research

Contact the HRPP for multi-site research (involving multiple institutions) and the details required for this section will be provided. Otherwise, indicate N/A.

N/A