PROJECT 2: EXPERIMENTAL MARKETPLACE, FLAVORS, AND NICOTINE CONTENT

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BACKGROUND, RATIONALE, AND CONTEXT

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) passed in 2009 provides the FDA with the authority to regulate tobacco products. One provision in this legislative act empowers the FDA to set limits on constituents in tobacco products, including nicotine. Such a measure has the potential to reduce the chance of individuals experimenting with smoking from becoming dependent and enable current smokers to quit when they are motivated to do so. Although the proposal to reduce nicotine in cigarettes has been met with skepticism by some because of concerns over compensatory smoking behavior and the potential emergence of a black market[1,2,3,4,5], this policy measure was considered to be technically feasible by the American Medical Association and the British Medical[6,7], by tobacco control researchers, policymakers and governmental officials who were convened in a meeting on nicotine regulation[8], and by the World Health Organization Study Group on Tobacco Product Regulation[9]. Most importantly, in July 2017, FDA Commissioner Gottlieb announced he was "directing our Center for Tobacco Products to develop a comprehensive nicotine regulatory plan premised on the need to confront and alter cigarette addiction." This announcement was followed on March 16, 2018 by the release of the Advance Notice of Proposed Rulemaking entitled "Tobacco Product Standard for Nicotine Level of Combusted Cigarettes" (ID: FDA-2017-N-6189-0001) "to obtain information for consideration in developing a tobacco product standard to set the maximum nicotine level for cigarettes."

Effects of Very Low Nicotine Content Cigarettes

Studies of very low nicotine content (VLNC) cigarettes (e.g., <2.4 mg/g) suggest that, acutely, they produce many effects in smokers that are qualitatively similar to normal nicotine content (NNC; e.g., 15.8 mg/g) cigarettes, but with somewhat reduced efficacy. VLNC cigarettes reinforce behavior[10,11] and maintain similar rates of self-administration as NNC cigarettes in brief sessions even though participants prefer NNC cigarettes when given a choice[11] Compared to not smoking, VLNC cigarettes increase ratings of satisfaction and liking[12,13,14], although the magnitude of these effects is typically reduced compared to those produced by NNC cigarettes[15,16,17]. VLNC cigarettes also reduce withdrawal and craving[18] although some symptoms (e.g., restlessness, impatience) may be more effectively alleviated by NNC cigarettes[19].

Studies in which VLNC cigarettes were utilized over a longer period suggest potential benefits in terms of reduced smoking. When only VLNC cigarettes were available in an inpatient setting, the number of cigarettes smoked and the motivation to smoke during periods of abstinence decreased over time[12]. Longer, outpatient studies have either found no change in smoking rates[20,21,22,13], or a significant decline in smoking rates. [23,24] Some studies have also shown that VLNC cigarettes reduce nicotine dependence[24] and increase quit attempts. [23] In one study conducted among individuals interested in quitting smoking, there was a significant increase in smoking cessation.[24]

There is very little evidence of adverse outcomes associated with VLNC use, including compensatory smoking. As noted above, data available to date indicate that the number of cigarettes smoked per day tends to decrease, not increase, over time. [23,13,24] Furthermore,

participants tend to reduce the volume of smoke inhaled and some studies have reported significant decreases in expired carbon monoxide (CO). [13,24] If compensatory smoking occurs, it appears to be short-lived[25,26] and may be more likely in heavily dependent smokers. [27] Likewise, few other unintended consequences have been identified. In our recent clinical trial, there was also no evidence of an increase in depressive symptoms among those with higher depression scores at baseline[28] and no evidence of an increase in alcohol or marijuana use. [29,30] However, individuals who were compliant with the VLNC cigarettes did gain weight over a six-week intervention period at a rate similar to what might be expected during smoking cessation. [31]

Most studies to date provide smokers with only two options: smoke study cigarettes (typically provided free to participants) or abstain from using tobacco, with clear instructions to not use non-study products. In this context, most smokers not only continue to smoke, but, despite instructions to the contrary, continue to use non-study cigarettes. Based on self-report, more than 75% of participants assigned to VLNC cigarettes use at least one non-study (normal nicotine) cigarette during trials that last 6 weeks or longer, typically smoking 2-4 non-study cigarettes on at least a third of the days.[23,32] Consequently, nicotine exposure (as measured by urine total nicotine equivalents) only decreases by about 60% compared to the 97% reduction of nicotine content in the product. [23] This pervasive noncompliance may attenuate the effects of VLNC cigarettes on abstinence[33], but it also may foreshadow how patterns of product use would evolve if nicotine product standards were enacted for combusted tobacco. Some may seek out black market cigarettes or tamper with cigarettes to increase nicotine delivery, but many others may turn to easily accessible alternative products.

Reducing the nicotine content of combusted products: the role of e-cigarettes

E-cigarettes have rapidly emerged as a commonly used non-combusted product in the U.S.[34, 35] with a proposed rule by FDA that it they be deemed a "tobacco product" and regulated as such.[36] A study by Hatsukami and colleagues showed that approximately half of all smokers switched to VLNC cigarettes will try e-cigarettes when provided the opportunity and that there is a negative association between smoking VLNC cigarettes and use of alternative products.[37] However, we know little about how the characteristics of e-cigarettes impact VLNC use and, conversely, how nicotine reduction in cigarettes impacts the use of e-cigarettes with different characteristics. Both nicotine and non-nicotine factors may be important.

Nicotine. Nicotine delivered via e-cigarettes may serve a variety of functions that support its actions as a reinforcer and an appealing alternative to smoking VLNC cigarettes. Some e-cigarettes can deliver as much or more (among experienced users) nicotine as a traditional cigarette with a relatively rapid rate of absorption (T max < 5 min).[38] This pharmacokinetic profile suggests that e-cigarettes may have greater positive reinforcing effects than VLNC cigarettes.[39] E-cigarettes can also be used throughout the day to maintain nicotine levels that would otherwise fall by 95% or more once participants start using VLNC cigarettes.[40] Indeed, e-cigarettes reduce withdrawal symptoms in cigarette smokers,[41-45] and this suppression is dependent on the nicotine concentration of the e-liquid.[45] Relatedly, greater nicotine delivery may also result in increased risk of dependence on e- cigarettes.[46] Finally, nicotine also acts peripherally on receptors in the oropharyngeal cavity which may contribute to sensory effects (discussed below) that might generalize across products. Together, these data suggest that e-cigarettes that more effectively deliver nicotine may be more likely to function as both positive and negative reinforcers and more able to compete with the reduced reinforcing effects of VLNC cigarettes.

Non-nicotine factors. E-cigarettes have a somewhat unique feature relative to other alternative products - they provide sensorimotor stimuli similar to combusted cigarettes, including a smoke-

like vapor and tobacco and other flavors. Decades of research highlight the importance of sensorimotor stimuli in maintaining behavior even when nicotine is absent.[47,48] Stimuli that have been associated with nicotine can elicit craving,[49] increase the probably of use,[50] increase positive subjective experiences,[51-54] reduce withdrawal,[53,55,56] and support behavior even in the absence of the drug.[57,58] These data suggest that the sensorimotor experience is an important determinant of whether a product will substitute for traditional cigarettes. E-cigarettes may serve this function better than other alternative products which might explain both why they were chosen most often in our pilot study (Overview D.2) and why they attenuate abstinence in cigarette users even if they do not deliver nicotine.[43]

E-cigarettes are available in a variety of flavors that may impact the appeal and reinforcing effects of the product. The full impact of flavors on e-cigarette use is still unknown, but it seems likely that the availability of non-tobacco flavors influences the likelihood of use. Recent estimates are that 53% of adults use e-cigarettes with flavors other than tobacco.[59] Other studies also supported this assumption, demonstrating that liquid flavor choices influence appeal and choice of e-cigarette device.[59, 60] If flavors impact the appeal of e-cigarettes, they may also impact the likelihood that smokers will switch from VLNC cigarettes to these products.

Measures for assessing product use and the impact of product characteristics

Behavioral Economics. Behavioral economics is an ideal framework for answering tobacco regulatory questions because it applies economic constructs such as product substitution and demand elasticity to individual product choice and decision-making. In behavioral economics, "price" is typically indicated in dollars but changes in price are also considered to be analogous to changes in effort required to obtain the product. The Cigarette Purchase Task (CPT) is an example of a behavioral economic assessment for smoking. In the task, participants are asked to indicate how many cigarettes they would purchase as the price of these products increases. From these data, a number of measures can be calculated including demand intensity (consumption at the lowest price) and demand elasticity (sensitivity to increases in price). A variation of the CPT is a cross-price task, which can be used to examine how changing the price of one commodity affects consumption of another commodity.

The Experimental Tobacco Marketplace (ETM) task is an extension of the cross-price task and allows researchers to examine the effects of cigarette price increases on alternative product purchasing within a complex tobacco marketplace. In this paradigm, participants use account balances to buy tobacco products from an online store. Across multiple task iterations, the price of cigarettes increases while the prices of the other tobacco products remain constant. Assessing cigarette substitution across multiple tobacco products is more informative to tobacco regulatory science than simple cross-price tasks because it more closely simulates real world decision-making from retailers selling multiple tobacco products. Recently, we conducted a pilot study using the ETM to examine the impact of a nicotine reduction policy on tobacco product purchasing.

Discrete Choice. Interdisciplinary research describes choice as a function of the relative expected value of the options at hand.[61, 62] Further, an option's anticipated value is derived from the integrated values of its individual attributes.[63, 64] Widely used in consumer research, discrete choice experiments (DCEs) reveal the extent to which individual product attributes determine choice.[65] In DCEs, across several trials, participants chose their preferred option from a selection of products, each described as a set of attributes. The products/combinations of attributes presented in each trial are experimentally varied such that the relative importance of each attribute can be discerned using logistic regression. In tobacco regulatory science DCEs have been used

frequently to evaluate general preferences for cigarette and vaping device characteristics.[66-69] Here, we will use the DCE method to investigate the contribution of nicotine content and flavor availability to choices between cigarettes and vaping devices.

OBJECTIVES

We are proposing a four condition ETM study to determine if banning NNC is sufficient for encouraging smokers to switch to potentially less harmful products or if the availability of higher nicotine and/or flavored alternative products (specifically e-cigarettes) are needed to achieve maximal reductions in smoking.

METHODS AND MEASURES

Overall Study Design

We propose to conduct a within-subjects, multi-session virtual lab study and validation field assessment to determine how the availability of flavored e-liquids affects product purchasing among cigarette smokers. Adult daily cigarette smokers (N=64) will be recruited for this study. After initial eligibility is assessed, participants will complete six virtual sessions (1 baseline, 4 experimental, and 1 follow-up) and three in person sessions with one field assessment to evaluate their tobacco use.

Design and Setting

Participants will be recruited from Winston-Salem, NC and the surrounding area using advertisements on public transit, community flyers, and social media.. In-person lab visits to drop off biosamples and pickup study products will be conducted at the Wake Forest Tobacco Control Center of Excellence located in Biotech Place in the Innovation Quarter.

Subject Selection Criteria

We anticipate recruiting up to 100 participants to achieve 64 completers.

Inclusion criteria:

1. 21+ years of age
2. Self-report smoking at least 5 cigarettes per day for the past year
3. Breathe carbon monoxide (CO) level > 8 ppm or positive urine NicCheck
4. Willingness to use other tobacco products during the study
5. Speak, comprehend, and read English sufficiently to complete study procedures
6. Have home access to a computer, smart phone, or tablet with a web camera and internet access
7. Tried a vaping device at least once in their lifetime

Exclusion criteria:

1. Currently seeking treatment to quit smoking
2. Self-reported serious medical or psychiatric condition(s) including cardiovascular and chronic respiratory diseases
3. Body temperature > 100.4 F

4. Cold, flu or COVID-19 symptoms including fever, cough, and runny nose in the past 30 days
5. Currently pregnant, breastfeeding or intending to become pregnant for the duration of the study or unwilling to agree to use adequate protection to avoid pregnancy
6. CO reading > 80 ppm

Those with unstable medical or psychiatric conditions are excluded as these symptoms could affect a participant's ability to complete the study and how they make decisions about what tobacco products to use. We will exclude those indicating immediate readiness to stop smoking, as participation in this study may not lead to reductions in smoking. We will exclude pregnant people, those trying to become pregnant and those currently breastfeeding due to the potential harmful effects of tobacco use on developing fetuses and infants. Because participants are required to complete portions of the protocol independently during the virtual lab sessions, they will need to be able to independently read and comprehend the study materials.

Those who report past 30 day cold, flu or COVID-19 symptoms will be temporarily excluded as a safety precaution. They will be able to re-screen once they have been symptom-free for more than 30 days.

Telephone Screening Survey

Interested individuals will complete a telephone screening interview. The screener will assess: current cigarette smoking; cigarette flavor preference; past 30 day use of tobacco products; pregnancy/breastfeeding; current health status, and intention to quit smoking. The interviewer will record the potential participant's responses in REDCap, web-based data collection platforms hosted by Wake Forest School of Medicine. The phone screening data will be used to establish preliminary eligibility. It will not be used for research purposes. Identifying information will be stored separately in a password-protected Excel spreadsheet on the Tobacco Control Center of Excellence server.

Potential participants will be instructed to show a valid, state issued photo ID during the virtual screening visit. Acceptable forms of identification include a Driver's License, State Photo ID Card, State Voter ID Card, Passport, or Military ID. If the potential participant does not have a valid, state issued photo ID, the interviewer can provide them with information on obtaining one. Participants will be given the option of receiving study information or visit reminders by phone, email, and/or text message.

A participant must complete their Virtual Visit 1 within 30 days of completing the Telephone Screening Survey. If the participant is not able to attend the virtual screening visit in that timeframe, they will need to complete the telephone recruitment questionnaire again but will maintain the same Subject ID number in the participant screening database.

Visits

Virtual Visit 1

Research staff will schedule video calls (e.g., WebEx or Zoom) with the participants. At their scheduled call time, research staff and participants will complete the consenting procedures (more information available below) and electronically sign the consent form via DocuSign. Participants will complete one verbal assessment with research staff via REDCap to collect their identifying information. Participants will then be sent a link to complete the eligibility surveys.

Research staff and participants will remain on video while the participant completes the REDCap survey. This will enable participants the ability to ask questions and share computer screens, if needed.

The following forms will be administered verbally by research staff via REDCap:

1. Identifying Information Form will include the participant's Subject Identifier, name, address (including the county of residence), email address, phone number, age, and date of birth.
2. Tobacco Use History and Exposure Questionnaire, which measures variables such as smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking.
3. Concomitant Medications Form will assess current medication usage.

The following screening surveys will be self-administered via REDCap:

1. Brief Medical History Questionnaire to query current diagnoses, symptoms and past health problems.
2. Demographic History Questionnaire, which will assess age, gender, ethnicity, race, education, income, marital status, living situation, and employment history.
3. Contemplation Ladder[34] to assess intention to quit smoking.

Fagerstrom Test for Cigarette Dependence[35] (FTCD) to assess nicotine dependence levels. In the event that the REDCap websites are not functioning, the virtual visits will be rescheduled to a later date and time.

Eligibility Determination

Research staff will determine eligibility after reviewing all criteria, sans the expired breath carbon monoxide reading and pregnancy test. Researchers will pay ineligible participants $20 for their time spent completing the screening surveys. Eligible participants will complete additional surveys and will receive an extra $10 for their time.

The following baseline assessments for eligible participants will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire,[36] which will assess past 14-day tobacco and nicotine product use. If a participant's reported cigarette use on the TLFB conflict with their reporting on the Tobacco Use History and Exposure Questionnaire, the RA will point out the discrepancy to the participant and ask whether they would like to modify their responses on the Tobacco Use History and Exposure Questionnaire or clarify why they are discrepant (e.g., participants had an upper respiratory infection in the past week that resulted in atypical smoking behavior).

The following surveys will be self-administered using REDCap:

1. Tobacco Policy Questionnaire (adapted from International Tobacco Control (ITC) – Four Country survey) which assess support for various tobacco control policies, including banning menthol flavoring in cigarettes and e-cigarettes.
2. Perceived Health Risks Scale, a measure of the perceived addictive potential and other health risks associated with cigarettes, e-cigarettes and nicotine gum
3. Tobacco Product Interest Scale, a visual analog scale assessing interest in use of various tobacco and nicotine products
4. Environmental/Social Influence on Tobacco use to assess environmental and social impacts on tobacco use.

In-Person Lab Visit 1

After completing Virtual Visit 1, participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. If participants do not have a mask, one will be provided to them to use for the remainder of the study. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner.

Participants will provide carbon monoxide (CO) readings at least 6-feet away from other people, including the research staff, while they have their masks off. NicCheck Strips, which assess cotinine levels in urine, will also be used to confirm smoking status if participants have an expired breath CO reading less than or equal to 8 ppm. Participants with child-bearing potential will complete a urine pregnancy test.

The following surveys will be self-administered using REDCap:

1. Minnesota Nicotine Withdrawal Scale a measure of nicotine withdrawal symptoms
2. Questionnaire of Smoking Urges-Brief – Usual Brand Cigarette, which measures the urge to smoke
3. Cigarette Evaluation Scale, which measures responses to cigarettes (e.g., reward, satisfaction)

Discrete choice task 1: The Sawtooth Lighthouse Studio platform will host a discrete choice task (See DCE Questionnaire). First, participants will rate the appeal of cigarettes and e-cigarettes characteristics, which helps familiarize them with the product features that will be manipulated in the choice task. Next, the choice task will begin, and they will make several choices between a cigarette option and an e-cigarette option responding to a prompt that asks which they would rather use exclusively for the next week. Each cigarette vs e-cigarette trial will present different combinations of cigarette nicotine content, e-liquid nicotine content, and e-liquid flavor. Finally, the participant will complete follow-up questions about which characteristics most informed their choices. The data from this task will reveal how participants prioritize and make tradeoffs between product type, nicotine content, and flavor when forming preferences.

After completing the discrete choice procedure, participants will also be given the opportunity to sample the low and normal nicotine Spectrum investigational cigarettes available during the ETM (up to 4 puffs each). Other products will also be available on the ETM, but will not be available for sampling. These include: fruit, dessert, menthol, and tobacco flavored e-liquids; and mint, fruit and cinnamon flavored nicotine gum.

Virtual Visits 2-5

Participants will complete Virtual Visit 2 between 1 and 21 days after completing In-Person Lab Visit 1. Virtual Visits 2-5 will ideally be conducted four days in a row to reduce online task fatigue. However, visits may be scheduled up to 7 days apart.

The following assessment will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire, which will assess tobacco and nicotine product use since their last virtual visit.

Participants will complete the ETM task on the computer. If the participant needs assistance with navigating the online marketplace the research staff may screen share and allow the participant to verbally select the items that they would like to purchase. The products available on the ETM include:

- Spectrum cigarettes
- Fruit, dessert, mint and tobacco e-liquids (e.g., Vaporesso Xross Mini)
- Mint, fruit, and cinnamon nicotine gum (e.g., Nicorette).

Participants will undergo one of four marketplace conditions during Virtual Visits 2-5, with the order of administration randomized across participants.

- Marketplace Condition 1 includes moderate nicotine content vape with all flavor e-liquids.
- Marketplace Condition 2 includes moderate nicotine content vape with tobacco e-liquids.
- Marketplace Condition 3 includes low nicotine content vape with all flavor e-liquids.
- Marketplace Condition 4 includes low nicotine content vape with tobacco e-liquids.

Staff will instruct participants to complete the ETM task as if they are purchasing the products from a retailer, and that one iteration of the task will be randomly selected and will determine which products they will use during the field assessment. In reality, we will randomly assign which condition is used (Condition 2 or 4) but will assign products based on when NNC were not available to simulate a nicotine content reduction policy.

For each marketplace condition, participants will complete 7 iterations of the ETM task in ascending order. The prices for NNC cigarettes on the ETM will be set at: $0.12, $0.25, $0.50, $1.00, $2.00 per cigarette; in the 1st ETM condition, NNC cigarettes will be set at $0.25 with no VLNC available to purchase to simulate current market status; while in the 6th ETM condition, NNC will be eliminated from the marketplace to simulate a nicotine content reduction policy. The costs for the other products will reflect average prices in NC and will not change during the task. For each task iteration, participants will receive individually-tailored account balances approximately equal to the money they would spend on cigarettes for seven days. They can purchase as many or few products as their account balance allows. Participants are not required to buy products from the ETM or can buy nicotine gum if they prefer. If they do not buy products from the ETM and do not use tobacco products during the field assessment, then they will receive their ETM account balance at Virtual Visit 6. This payment is delayed to reduce the likelihood that they will use this money to buy their preferred brand cigarettes, thus decreasing the validity of the ETM task.

Participants will be instructed to use only the products purchased from the ETM during the subsequent 7-day period after Virtual Visit 5 and told that we will assess adherence at Lab Visit 3.

In-Person Lab Visit 2

In-Person Lab Visit 2 will be completed up to 48 hours after completing Virtual Visit 5. Participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment during the visit including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner.

Participants will provide CO readings be at least 6-feet away from other people, including the research staff, while they have their masks off.

Participants will be given the products they purchased during the ETM task and will be instructed to only use these products for the next seven days. They will also be given a urine collection cup and instructions for sample collection.

The field assessment validates the ETM task by having participants use the products in the real world, simulating the different regulatory environments. Actual product use enables us to measure their subjective experiences such as withdrawal, craving, or product satisfaction as well as assess changes in carbon monoxide exposure, a biomarker of harm, when using products other than menthol cigarettes. We will conduct between-subjects analyses comparing these secondary outcomes by marketplace condition.

Virtual Visit 6

Participants will complete Virtual Session 6 seven days after completing In-Person Lab Visit 2.

The following baseline assessments will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire which will assess past tobacco and nicotine product use since Virtual Visit 5.

The following surveys will be self-administered using REDCap:

1. Tobacco Policy Questionnaire
2. Minnesota Nicotine Withdrawal Scale
3. Questionnaire of Smoking Urges-Brief – Usual Brand Cigarette
4. Product Evaluation Scale – VLNC, E-Cigarette, Gum (whichever product(s) they select)
5. Perceived Health Risks Scale
6. Tobacco Product Interest Scale
7. Health Changes Questionnaire

Participants will complete the ETM task under the same marketplace condition from which they received their field assessment products. Exploratory pre-post field assessment analyses will examine how actual use of the products affects subsequent purchasing of those products.

Research staff will conduct in-depth interviews with the participants to assess the following constructions: 1) decision-making during the ETM task; 2) use of alternative products during the field assessment; 3) product risk perceptions and; 4) opinions regarding possible tobacco control policies.

In-Person Lab Visit 3

In-Person Lab Visit 3 will be completed up to 48 hours after completing Virtual Visit 6. Participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment during the visit including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner. Participants will bring a first void urine sample, which will be banked for future biomarker analysis (e.g., total nicotine equivalents) and all of their used/unused products.

Participants will provide CO readings at least 6-feet away from other people, including the research staff, while they have their masks off. Participants will complete a second iteration of discrete choice task 1. Data from the two choice tasks will be compared within participants to see whether product use affected preferences.

All participants will be emailed a cessation manual and local smoking cessation resources.

Product adherence

To verify self-reported tobacco use, all used and unused products will be collected and counted at In-Person Lab Visit 3. Discrepancies between consumption stated on the TLFB versus consumption based on the products returned will be addressed. Non-adherence (i.e., using products not purchased from the ETM) will be assessed via the TLFB and qualitative interview with the importance of honest self-reporting emphasized. If participants report not using combusted tobacco, then CO readings < 6 ppm will verify their self-report.

Compensation

Participants will be paid $160 for completing the study. They will earn $30 for completing Virtual Visit 1, $15 per visit for completing Virtual Visits 2-5, $20 for Virtual Visit 6, plus a $50 bonus for completing the study. Participants who do not meet enrollment criteria at Virtual 1 will earn $20 for attending the visit. Participants who start but do not complete the study will receive payments for the virtual visits attended. They will not receive the $50 completion bonus. Participants will also be reimbursed up to $20 per in-person lab visit for transportation costs.

ANALYSIS PLAN

Primary Outcome

- Number of cigarettes purchased (analyzed as raw data and using derived behavioral economic measures).

Secondary Outcomes

- E-liquid purchased (analyzed as raw data and using derived behavioral economic measures).
- Relative importance and utility data from discrete choice experiment
- Perceived Health Risk Scale scores
- Product Evaluation Scale scores
- Minnesota Nicotine Withdrawal Scale scores
- Questionnaire on Smoking Urges scores
- Tobacco Product Interest scores
- Tobacco Policy Questionnaire scores

Exploratory Outcomes

- Themes emerging from the qualitative interviews
- Product use during Field Assessment
- Biomarkers of exposure during Field Assessment

Sample Size/Estimation/Analysis

Statistical analysis plan

This ETM study will use a 2x2 factorial design. The primary objective will be to evaluate the effect of the two factors – e-liquid nicotine content (moderate vs. low) and e-liquid flavors (all flavors available vs. only tobacco flavor) – on purchasing behavior during virtual visits 2 – 5. Product use behavior, biomarkers of exposure, and other measures of smoking behavior during the field assessment will be evaluated in exploratory analyses.

Analysis of the Primary Outcome

The primary outcome will be the number of cigarettes purchased during the virtual visits. These data will be analyzed both in their raw form (i.e. the raw number of cigarettes purchased) and using derived behavioral economic measures. This is a within-subject design, with each participant providing data under all four factor combinations, and, for the raw data, each participant will be provide data for all price combinations nested within a visit.

Raw data will be analyzed using a linear mixed-effects model that includes main effects for e-liquid nicotine content (low vs. moderate), e-liquid flavors (all vs. tobacco only), visit, price condition (analyzed as a categorical variable), and a carryover effect for the previous visits condition (treated as a four-level categorical variable, and random effects for participant and visit nested within participant. This will account for correlation from multiple observations from the same participant, both within and across visits. We will also evaluate whether there is an interaction between the e-liquid nicotine content and e-liquid flavors factors. If significant, the interaction will be included in the model; otherwise, it will be removed. The analysis of derived behavioral economic measures will follow an analogous approach, except that for each measure, there will only be a single outcome for visit. As a result, our linear mixed-effects model will not include a main effect for price condition, and there will only be a single random effect for each participant. Behavioral economic measures will be derived by generating demand curves using an exponential demand equation. Specific measures considered will include: Alpha - the rate of change in demand, and Q_0 – peak consumption. For all analyses, assessments of key model assumptions will be completed and we will considering transformations or alternate analytic approaches if these assumptions are violated.

Analysis of Secondary Outcomes

The analysis of secondary endpoints will be analogous to the analysis described above for the primary endpoints. The amount of e-liquid purchased will be analyzed both as the raw data for each price condition and using derived behavioral economic measures. The analysis of these endpoints will be completed using linear mixed-effects models with the fixed and random effects terms described above. The analysis of the various scales and scores collected at each visit will follow the same approach as the analysis of derived behavioral economic measures described above. As before, assessments of key model assumptions will be completed and we will considering transformations or alternate analytic approaches if these assumptions are violated.

Cross-price elasticity estimates will be calculated as the slope of the regression line (B_1) fit to log-transformed purchasing of each alternative product when offered at fixed prices (C) versus log-transformed menthol cigarette price (P): $\log C = B_0 + B_1 \log P$. Exploratory paired t-tests will compare product purchasing during the pre- and post-field assessment ETM task.

Attribute-importance will be generated from discrete choice response data using logistic regression. A utility range (the difference between a characteristics highest and lowest estimated part-worth utility) will be calculated for device type, cigarette nicotine content, vaping device nicotine content and vaping device flavor availability. Part-worth utility refers to the relative

contribution of each level of a product characteristic on choice (ie, as approximated by the estimated coefficients in the model). The relative importance of each characteristic on making a choice will be calculated as the utility range for each characteristic, divided by the sum of all the characteristics' utility ranges.

Analysis of Exploratory Outcomes

Product use and biomarkers of exposure during the field assessment will be analyzed using linear regression or other appropriate regression models. The model for primary analysis of these data will include main effects for each of the two factors (for the ETM condition carried into the field assessment), and the corresponding baseline measure to improve precision. We will also test the two-way interaction between the two factors. If significant, the interaction will be included in the model; otherwise, it will be removed. We will also complete a secondary analysis that adjusted for age, race, sex, and other covariates that vary between treatment conditions. Biomarkers of exposure will be natural-log-transformed before analysis due to skewness. Key model assumptions will be evaluated for other endpoints and appropriate transformations will be considered if model assumptions are violated.

For the qualitative data, we will use grounded theory to develop hypotheses related to the topics of interest. Interviews will be audio-recorded and transcribed verbatim. Audio transcriptions will be reviewed for accuracy and entered into Atlas.ti or another qualitative data management software program. Two research staff members will code the first five interviews to achieve greater than 90% interrater reliability and then every 10th interview to ensure integrity. The research team will analyze the interviews using iterative analyses including qualitative research techniques of open and axial coding; major thematic categories; analytical domains; triangulation of data; comparisons within and between groups; and documenting analytical pathways. Saturation will be achieved when no new themes emerge.

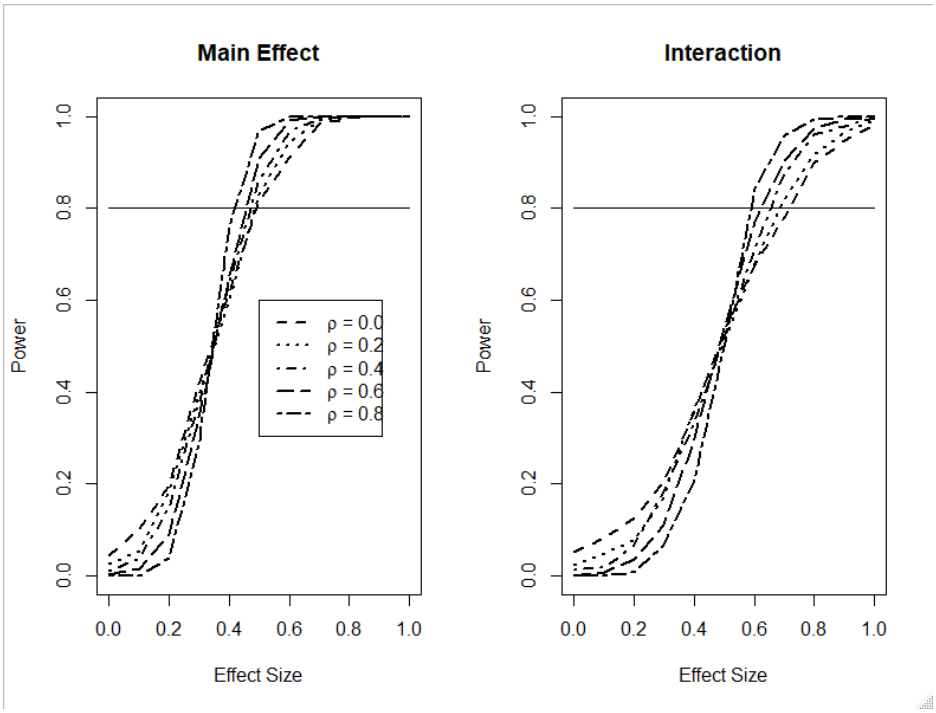
Missing Data

Study staff will make every effort to minimize missing data in the proposed study. Nevertheless, we plan to complete a sensitivity analysis to evaluate the impact of missing data on trial conclusions. We will compare subjects with and without missing data in order to identify baseline covariates associated with missing data. Our primary approach to handling missing data will be multiple imputation where missing values are imputed using regression models developed from baseline covariates (Little and Rubin, 2002). In addition, we will conduct a sensitivity analysis of the primary and secondary endpoints using a complete-case analysis, baseline-carried-forward and last-observation carried forward. The results of these analyses will be compared to the primary analysis to evaluate the robustness of our conclusions.

Power calculation

Our objective is to enroll 64 completers, and we will test the main effects for e-liquid nicotine content, e-liquid flavors, and the interaction in a within-person design. In a within-person design, the power will depend heavily on the intra-participant correlation, which is unknown ***a priori***. To evaluate the power, we simulate our trial under various assumptions regarding the effect size for the main effects and interactions, and the within-participant correlation (see Figure below). For the main effects of e-liquid nicotine content and e-liquid flavor, we have 80% power to detect an effect size of approximately 0.45 with a moderate within-participant correlation of 0.4, which ranges from approximately 0.49 with a within-participant correlation of 0.0, to 0.41 with a within-participant correlation of 0.8. For the interaction, we have 80% power to detect an effect size of

approximately 0.65 with a moderate within-participant correlation of 0.4, which ranges from approximately 0.75 with a within-participant correlation of 0.0, to 0.56 with a within-participant correlation of 0.8.



HUMAN SUBJECTS PROTECTION

Recruitment Methods

Participants will be recruited by posting study information on flyers distributed in the community, Craigslist, social media channels, and Wake Forest Baptist's "BeInvolved" site. Members of the PI's research team will perform recruitment. Coordination of potential participants' virtual visits will be done by phone or by email. Contact information will be stored on password-protected computers that are kept behind locked doors for which only the PI's research team will have access keys and passwords.

Recruitment will be continuous through the course of the study. If necessary, advertisements and recruitment strategies will be redesigned to target specific sub-populations if recruitment falls short of a representative demographic balance.

Participants that have previously performed research with the PI and co-investigator research team and have agreed to be re-contacted for future studies may be contacted for recruitment purposes by email or phone according to their previously stated preference.

Informed Consent

Prior to Virtual Visit 1, participants will be briefly screened over the phone to determine initial eligibility. For this process alone, we will seek a waiver of signed informed consent. This part of the research procedure presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Before beginning the informed consent process during Virtual Visit 1, participants will need to show a valid, state issued photo identification. The interviewer will confirm the age and identity of the participant via video (e.g., WebEx, Zoom). The interviewer will then present a PowerPoint via screen share of the main takeaways of the informed consent form. Participants will be asked follow up questions to ensure comprehension of the informed consent form.

In order to ensure adequate informed consent, participants will be asked to read the first several lines aloud to determine literacy. If the interviewer determines that the participant is not literate, they will be dismissed from the study but will receive $20 for attending the screening visit. The participant will be instructed to read several open-ended questions aloud and discuss the answers with the researcher. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and his/her rights as a research participant will the consent form be signed electronically via DocuSign and the participant undergo screening procedures. The participant will be emailed a signed electronic copy of the consent document for their records.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed *(*three years after closure of the study; paper documents will be shredded, electronic documents will be securely deleted using software that will delete and overwrite sensitive disk space*),* consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data Safety and Monitoring

The principal investigator and co-investigators will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator and co-investigators will be assisted by other members of the study staff.

Potential risks of participation

1. Survey Questionnaires: The interviews will include questions about medical history, tobacco use, and questionnaires about mood. Answering these personal questions could make the participant feel uncomfortable.
2. Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.

3. Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to severe or fatal medical problems including:
    a. Cardiovascular diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    b. Respiratory diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
    c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia
    d. Diabetes
    e. Abnormal immune function, rheumatoid arthritis
    f. Other health risks including but not limited to infertility, ectopic pregnancy, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction, age-related macular degeneration, blindness and cataracts.
4. Use of Vaping Devices: can exposure users to several chemicals including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-liquids, including solvents, flavorants, and toxicants, are not completely understood. Vaping device aerosol is not harmless "water vapor" although it generally contains fewer toxicants than combustible tobacco products. Specific potential known risks include
    a. Vaping devices contain nicotine which may contribute to some of the disease associated with smoking
    b. The most common side effects related to vaping devices are changes in taste, mucus in throat/sinus, dry mouth, dry cough, throat irritation, sore throat, mouth ulcers, dizziness, headache, and nausea.
    c. On rare occasions, batteries from vaping devices have exploded/ignited and injured users
    d. Vaping devices can overheat and present minor burn risks if the button is turned on repeatedly. Participants are told to be careful if storing the device in a place where the button might accidentally be pressed often.
    e. Ingestion of e-liquids containing nicotine can cause acute toxicity and possible death if the content of the cartridges containing nicotine are consumed.
    f. Participants are told to keep study vaping devices and all e-liquids away from children and pets.
5. Use of Medicinal Nicotine: Most common adverse effects for medicinal nicotine include irregular heartbeat/palpitations, high blood pressure, mouth sores, mouth or throat irritation, heartburn, upset stomach, vomiting, diarrhea, dizzy or lightheadedness, and hiccups or belching. Additional adverse effects associated with nicotine gum include teeth or jaw problems. There may also be a risk of nicotine toxicity including symptoms such as nausea, dizziness, vomiting, diarrhea, and weakness.
6. Dual use of tobacco or nicotine products: There is also the chance of use of more than one product and/or continued use of the products; however, cessation of all tobacco products will be strongly recommended to the participants at the end of the study.
7. Smoking Withdrawal: Participants may experience smoking withdrawal symptoms during this study if they decide not to purchase tobacco products. The symptoms can be uncomfortable but are typically of minimal risk. Smoking withdrawal symptoms include:
    a. Anger, irritability, frustration
    b. Anxiousness, nervousness
    c. Depressed mood or sadness
    d. Desire or craving to smoke
    e. Difficulty concentrating

f. Increased appetite, hunger or weight gain
g. Insomnia, problems sleeping or waking at night
h. Restlessness
i. Impatience
j. Constipation
k. Dizziness
l. Coughing
m. Dreaming or nightmares
n. Nausea
o. Sore throat

8. Returning to Regular Smoking: It is possible that if participants return to smoking their usual brand of cigarette at the end of the study they may experience mild and transient nausea, dizziness, and lightheadedness.
9. Changes in Mood, Emotions and Psychiatric Symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine use or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
10. Smoking and Oral Contraceptives in Women: Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking.

Avoiding Risks during Pregnancy

Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, birth defects, and other problems. To avoid risks to the participant and fetus, female participants will be tested for pregnancy at the Screening Visit.

Expected benefits of participation

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

Reporting Unanticipated Problems, Adverse Events or Deviations

Identifying Adverse Events

While participating in the study, adverse events will be assessed at Virtual Visit 6 and carbon monoxide levels from In-Person Lab Visit 3. Adverse events will typically be identified during the administration of the Health Changes Questionnaire. Other adverse events may be identified by spontaneous reports from the participant. Withdrawal symptoms are considered an adverse event if the symptom had a significant impact on the participant's daily life, caused a major disruption of functioning, or took any medication for it.

- Health Changes Questionnaire: If the participant answers "YES" to Questions 1, 2, or 3 the interviewer should assess for adverse events.
    1. Have you had any negative changes in your physical or mental health since your last virtual visit? If yes, briefly describe.

2. Since your last virtual visit, have you received any form of medical care? If yes, briefly describe.
3. Have you had any changes in medication since your last visit?

Physiological data that will be reviewed:

1. CO level: The 'Adverse Event Form' will be completed if the average of two (or three) consecutive measurements in the same visit is:
    - CO is greater than 50 ppm if CO at Screening/Baseline Visit is < 20 ppm.
    - CO is greater than 60 ppm if CO at Screening/Baseline Visit is 20 – 34 ppm.
    - CO is greater than 70 ppm if CO at Screening/Baseline Visit is 35 – 49 ppm.

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1. Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2. DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
3. Suicide Attempt: A participant will be withdrawn if they attempt suicide at any time during participation in the study
4. Psychiatric Hospitalization: A participant will be withdrawn if they are hospitalized for psychiatric reasons at any time during participation in the study.
5. Pregnancy: If a participant indicates they are pregnant at Virtual Visit 6 or In-Person Lab Visit 3, they will be withdrawn from the study, and this event will remain open until delivery. At that time the license medical monitor will contact the participant to ask a few questions about the baby's health and will update the open 'Adverse Event Form'.

The following will be monitored and can lead to the participant being withdrawn by the PI:

1. Expired breath CO >80 ppm
2. Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical monitor to determine whether continued participation in the study is appropriate.
3. If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then the PI can withdraw them from the study at the PI's discretion.
4. If a participant fails to attend her/his Virtual Visit 1 within the 21-day allowable visit window, they will not be eligible to reschedule the visit or continue participation in the study.

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