Examining the Appeal of Nicotine Pouches in Ohio Appalachia

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1. Background Information and Rationale

Abbreviations and Definitions of Terms

Term	Definition	Abbreviation
Nicotine Pouches	Nicotine pouches are white pouches that contain nicotine and are likened to tobacco-free snus.	NPs

Appalachia, Ohio	32 rural counties in Ohio that are markedly different when defined by poverty, health, education, and access to resources within the state.	Appalachia
Pharmacokinetics	Study of drugs within the body.	-
Smokeless tobacco	Also called chew, dip, or snuff, this tobacco product is chewed rather than smoked.	SLT
Adverse event	Any mild reaction to the product including a headache, trouble sleeping, dizziness, or nausea.	AE
Serious adverse event	A serious reaction or breach in confidentiality.	SAE
Center for Tobacco Research	The Center for Tobacco Research provides evidence-based knowledge surrounding the regulation of tobacco products to inform individual health decisions as well as public health regulations.	CTR
Inclusion/Exclusion	Criteria that the participant must meet or not meet in order to be considered for the study.	I/E
Early Termination	When the participant is removed from the study at the discretion of the PI.	ET

Introduction

Abstract

Nicotine pouches are novel smokeless tobacco products that are marketed as substitutes for cigarettes and gaining in popularity. They may have high appeal in Ohio Appalachia, a region with high prevalence of smoking and a population disparately impacted by tobacco-associated cancer. There is little research on the abuse liability of nicotine pouches (i.e., the likelihood of sustained patterns self-administration) in Ohio Appalachia to understand their appeal and potential impact on public health and tobacco-related disparities. This study is designed to estimate the abuse liability of nicotine pouches with varying nicotine concentrations relative to cigarette smoking in a clinical study with Appalachian smokers. This pilot will provide the foundation for a line of research that can inform policy locally and nationally. Dissemination of

our results through community partners will inform efforts to reduce tobacco-associated cancer disparities in Ohio Appalachia.

Background

Tobacco use is a public health threat in the United States (U.S.),[12] particularly in Appalachian regions.[1] Declines in the prevalence of tobacco use in Appalachia have not mirrored the rest of the country,[13] leading to widening disparities in cancer.[5,6] Reasons for the high prevalence of tobacco use in Appalachia include social norms supporting tobacco use in the home;[14] viewing tobacco use as a rite of passage;[2] a history of economic reliance on tobacco farming;[14] promotion of smokeless tobacco (SLT) use in situations when cigarette smoking is unsafe (e.g., coal mining);[15] and marketing that reinforces Appalachian cultural values of individuality and ruggedness.[2,16]

Nicotine pouches (NPs; e.g., On! and Zyn) are a novel form of SLT that is rapidly gaining market share in the U.S.[7] NPs come in containers with 15 to 20 sachets containing nicotine, flavoring, and other ingredients that are placed between the upper gum and lip (**Figure 1**). The one published study characterizing the contents of NPs has reported that they likely confer similar harm to nicotine replacement therapy.[8] Moreover, in comparison to snus, a form of SLT, NPs contained lower levels of metals (arsenic, cadmium, chromium, lead, nickel) and carcinogens NNK, NNN, acetaldehyde, and ochratoxin.[8] This is notable because the Food and Drug Administration recently authorized some brands of snus to be marketed modified risk tobacco products because they pose less harm than cigarettes.[17] Based on this evidence NPs may offer an opportunity for tobacco harm reduction in Ohio Appalachia—as long as they appeal to smokers and encourage complete smoking cessation.

Figure 1. Example of NPs.

Key components of a tobacco product's appeal are how it is marketed, how it is perceived by consumers, and how effectively it delivers nicotine. An estimated 90% of direct-mail NP advertisements positioned NPs as a substitute for cigarettes or other tobacco products, 70% included claims that NPs could be used anywhere, and 42% included implicit reduced harm claims.[10] In other words, NPs are being marketed as less harmful, situational substitutes for cigarettes, but little is known about how smokers perceive NPs and their marketing. Regarding nicotine delivery, one NP brand with a high nicotine concentration has similar nicotine delivery to one brand of moist snuff.[9] However, moist snuff has widely variable nicotine delivery,[4] and it is unknown how nicotine delivery of NPs compares to cigarettes. The limited research on the abuse liability (i.e., appeal and addictiveness) of NPs suggests that they may be substitutes for cigarettes based on how they are marketed and deliver nicotine. However, it is unknown whether NPs will encourage or be perceived as useful for smoking cessation among smokers in Ohio Appalachia, a region with disproportionately high prevalence of smoking and disparately impacted smoking-related health outcomes.

Most of the research describing tobacco use in Appalachia is at least a decade old and little is known about the appeal of novel tobacco products, like NPs, in this region. NPs might hold harm reduction potential for smokers in Ohio Appalachia if they completely switch to NPs,

but it is also possible that NPs could increase the public health harms of smoking if they are used as situational substitutes for cigarettes. In this case, they could maintain or increase nicotine dependence and ultimately result in little change in exposure to tobacco toxicants.[11]

Furthermore, synthetic "tobacco-free" nicotine products (i.e., products that use chemically-derived rather than tobacco-derived nicotine) are rapidly proliferating, and it is unclear whether there is any available regulatory action that the US FDA can take to stop it. FDA's regulatory authority over tobacco products was provided by the Family Smoking Prevention and Tobacco Control Act of 2009 (FSPTCA), which defined tobacco products as any product "made or derived from tobacco." Therefore, new tobacco-free synthetic products may not fall under the FDA's purview as they are not legally tobacco products. Consequently, many recent FDA tobacco rulings to help curb tobacco use, especially among youth and young adults (Tobacco 21, e-cigarette flavoring bans, etc.), may be completely side-stepped and lead to the unfettered manufacture and sale of synthetic nicotine products. Making matters worse, it is unclear what the unregulated sale of synthetic nicotine products may mean for public health. The scientific evidence is severely limited as to its impact on user perceptions, behaviors, addiction, and health.

Understanding the pharmacokinetic and subjective results of tobacco-derived NPs when compared to cigarettes (Aim 1) and tobacco-derived vs. synthetic NPs (Aim 2) among adult cigarette smokers is critical in this new landscape of tobacco use.

Description and Rationale of Intervention

Aim 1: This study will estimate the abuse liability of NPs with varying nicotine concentrations relative to cigarette smoking in a clinical study with Ohio Appalachian smokers by using a randomized crossover experimental design. Over the course of three clinic visits, N=40 adult cigarette smokers who live in Ohio Appalachia will: 1) smoke a usual brand cigarette, 2) use a 3mg nicotine concentration NP, and 3) use a 6mg nicotine concentration NP in our clinic; only one tobacco product will be used at each visit. We will measure nicotine pharmacokinetics, subjective effects, and intentions to use and switch to NPs. Our hypotheses are that (1a) both NPs will deliver less nicotine, and deliver it more slowly, than cigarette smoking and (1b) the 6mg nicotine NP will have greater nicotine delivery, be rated as more appealing, and have greater intentions for future use than the 3mg nicotine NP.

Aim 2: This study will examine the subjective and pharmacokinetic differences between tobacco-derived and synthetic NPs in adult cigarette smokers by using a randomized crossover experimental design. Over the course of three clinic visits, N=15 adult cigarette smokers who will: 1) use a 3mg tobacco-derived Zyn brand NP, 2) a 3mg synthetic Fre brand NP, and 3) a 3mg Niin brand synthetic NP in our clinic; only one product will be used at each visit. We will measure nicotine pharmacokinetics, subjective effects, and intentions to use and switch to NPs. Our hypotheses are that (1) tobacco-derived NPs will deliver nicotine more quickly and effectively than the synthetic NP and (2) the tobacco-derived NPs will be rated as more appealing and have greater intentions for future use than the synthetic NPs.

Intervention Impact

Aim 1:NPs are a novel tobacco product with potential to reduce or increase the harm of tobacco use in Appalachia. Evaluating NP abuse liability among Appalachian smokers will clarify the public health effect of NPs in Appalachian Ohio. Results will inform public health efforts, policy, and clinical care aimed at reducing tobacco-related disparities in Appalachia.

Aim 2: The difference between tobacco-derived and synthetic NP on NPs' abuse liability is unknown. Tobacco-derived nicotine contains >99% of the *S* stereoisomer of nicotine, but most methods of manufacturing synthetic nicotine result in a racemic mixture of *R*- and *S*-nicotine stereoisomers.[78] NP manufacturers (as well as e-cigarette manufacturers including Puff Bar) that claim to use synthetic nicotine do not specify whether their nicotine solutions contain the racemic *R-/S*-nicotine mixture, or if *R*-nicotine is omitted. Although less studied than S-nicotine, it is speculated that *R*-nicotine produces weaker biological effects because it is a 10-fold less potent agonist of nicotinic receptors.[78] In other words, we expect that NPs using synthetic nicotine vs. tobacco-derived nicotine will have a lower abuse liability—potentially making them less substitutable for cigarette smoking. Results from this work will provide the first evaluation of synthetic nicotine delivery via oral tobacco, informing public health efforts, policy, and future research in this emerging area of tobacco control.

Preliminary Research

For preliminary research, we evaluated characteristics of Appalachian adults enrolled in the Tobacco User Adult Cohort study. Compared to non-Appalachian tobacco users, Appalachian tobacco users initiated tobacco use and became regular users approximately one-year earlier, used tobacco more frequently, and had lower interest in cessation.[15] Investigations into dual use found that a majority of Appalachian adults who used cigarettes and e-cigarettes were likely to transition to using cigarettes exclusively.[37] In other words, it appears that e-cigarettes were being used unsuccessfully by smokers trying to quit and that they were an inadequate complete substitute for smoking. Additionally, exclusive e-cigarette users were more likely than dual users to report that e-cigarettes are useful for quitting smoking and that e-cigarettes feel like smoking regular cigarettes.[38] *Conclusions: (1) Tobacco use behaviors vary between Appalachian and non-Appalachian adults, and thus evaluation of our research objectives in Ohio Appalachia is warranted; (2) uptake of novel tobacco products for smoking cessation (i.e., complete substitution) has been largely unsuccessful in Ohio Appalachia; and (3) exclusive use of novel tobacco products in Appalachia is associated with beliefs that the product is appealing and aids in smoking cessation.*

We are also conducting a pilot observational study examining awareness of NPs, NP use, and exposure to NP marketing in Ohio adults. To date, we have enrolled 294 participants (32% smokers, 45% SLT users, 23% non-users) to complete a brief, online survey. Of the sample, 92% have agreed to be re-contacted for future studies—providing a source of recruitment for our proposed pilot. In preliminary analyses, nearly two-thirds (66%) of participants were aware of NPs, 38% had tried NPs, and 31% reported current NP use. Among smokers, awareness (65%) and trial (33%) of NPs were similar to the overall sample, and 25% reported current use. NP marketing exposure among smokers was also high (65% in the past year), with the most common sources of exposure being point of sale (35%), online/social media (29%), and

television (20%). *Conclusions: 1) Awareness and trial of NPs is growing among Ohio adults, including cigarette smokers; and 2) marketing exposure is common, supporting our rationale to extend this line of investigation to understand NP appeal and addictiveness in smokers in Appalachia.*

Aim 1 Study Objectives

Primary

- To estimate the abuse liability of NPs with varying nicotine concentrations relative to cigarette smoking.

Secondary

- To clarify the public health effect of NPs in Appalachian Ohio.

Exploratory

- To estimate the abuse liability of NPs with varying nicotine concentrations relative to cigarette smoking by measuring nicotine pharmacokinetics.
- To estimate the abuse liability of NPs with varying nicotine concentrations relative to cigarette smoking by measuring subjective effects.
- To estimate the abuse liability of NPs with varying nicotine concentrations relative to cigarette smoking by measuring intentions to use and switch to NPs.

Aim 2 Study Objectives

Primary

- To understand the pharmacokinetic difference between tobacco-derived and synthetic NPs.

Secondary

- To clarify the public health effect of NPs on adult smokers

Exploratory

- To understand the differences in abuse liability between tobacco-derived and synthetic NPs by measuring nicotine pharmacokinetics.
- To understand the differences in abuse liability between tobacco-derived and synthetic NPs by measuring subjective effects.
- To estimate the abuse liability of tobacco-derived vs. synthetic NPs by measuring intentions to use and switch to NPs.

2. Investigational Plan

Study Outline

This study will recruit 40 adult cigarette smokers from Ohio Appalachia and surrounding rural areas (Aim 1) and 20 adult cigarette smokers from Ohio (Aim 2) for a randomized crossover study. Subjects will be recruited through social media advertisements; through our nicotine pouch pilot study, where participants agreed to future contact regarding other studies; and through outreach to our community partners: the OSUCCC's Community Outreach and

Engagement team and the Tobacco Free Ohio Alliance. Subjects will have an initial phone screen to confirm interest and eligibility and will then be invited to participate in 3 study visits in person visits at the Center for Tobacco Research.

Aim 1: Order of study clinic visits will be randomized. In random order, participants will 1) smoke one usual brand cigarette, 2) use one 3mg NP, and 3) use one 6mg NP. Research staff will measure nicotine pharmacokinetics, subjective effects, and intentions to use and switch to NPs through physiological data, lab values, and questionnaires.

Aim 2: Order of study clinic visits will be randomized. In random order, participants will use 1) Zyn wintergreen 3mg (tobacco-derived nicotine) 2) a Fre wintergreen 3mg (synthetic nicotine), and 3) a Niin wintergreen 3mg (synthetic nicotine). Research staff will measure nicotine pharmacokinetics, subjective effects, and intentions to use and switch to NPs through physiological data, lab values, and questionnaires.

Recruitment phase

Aim 1: We will recruit daily cigarette smokers who live in Ohio Appalachia and surrounding rural areas using social media advertisements, by re-contacting participants from our preliminary studies who agreed to take part in future studies, and through outreach via our community partners.

Geographically, recruitment advertising will be targeted to Ohio Appalachia counties (32 in total), surrounding rural counties close to Ohio Appalachia, with efforts focused on counties within one hour of Columbus.

Aim 2: We will recruit daily cigarette smokers using social media advertisements, by re-contacting participants from our preliminary studies who agreed to take part in future studies, and through outreach via our community partners.

Participants in Aim 2 may reside anywhere in Ohio, though recruitment efforts will be focused within one hour of Columbus.

Screening and scheduling phase

Interested participants will fill out a brief questionnaire to confirm eligibility either online or over the phone with research staff. Participants will be asked a series of questions regarding their tobacco product usage, health status, willingness to travel to Columbus for study visits, and brief demographic and contact information. Research staff will review the screener questionnaire for eligibility and inform participants if they are eligible for this study or not. Research staff will provide a study overview, discuss study procedures, and ascertain participant interest. Should the participant wish to proceed, research staff will schedule the first visit and communicate IRB-approved guidance, such as the CTR address and the need for subjects to abstain from tobacco products for 12 hours prior to the study visit. Participants will be advised that each research visit must be scheduled 2 or more days apart and that they must bring their own brand of cigarettes to the study visits in case they are randomized to smoke cigarettes at a particular visit.

Clinic Visits

Aim 1: Participants will be invited to the CTR to complete study procedures. At visit 1, informed consent will be collected. During visits 1-3, participants will complete an exhaled CO test, take a pregnancy test if applicable, a line will be placed for IV blood draw by the staff research nurse for IV blood draws throughout the course of the study visit, and be asked to either smoke their usual brand or insert a 3mg or 6mg NP and then sit in the room for 60 minutes. At each visit, participants will be randomly assigned to use 3mg Wintergreen pouches, 6mg Wintergreen pouches or their own brand of cigarettes. Participants will be asked a series of 3 questionnaires before, during, and after each product is used. Blood draws will be collected from the line at 0 5, 15, 30, 60, and 90-minutes. 3mLs, or a little less than 1 teaspoon, of blood will be drawn at each timepoint.

Measures of craving and withdrawal relief will be assessed at each blood draw (see attached surveys). If a collection interval is not met there will be no draw retroactively. Participants will be assessed for AE throughout procedures and prior to leaving the visit.

Aim 2: Participants will be invited to the CTR to complete study procedures. At visit 1, informed consent will be collected. During visits 1-3, participants will complete an eCO test, take a pregnancy test if applicable, a line will be placed for IV blood draw by the staff research nurse for IV blood draws throughout the course of the study visit, and be asked to either try a 3mg NP or a synthetic NP and then sit in the room for 60 minutes. Participants will be asked a series of 3 questionnaires before, during, and after each product is used. Blood draws will be collected from the line at 0 5, 15, 30, 60, and 90-minutes. 3mLs, or a little less than 1 teaspoon, of blood will be drawn at each timepoint.

Measures of craving and withdrawal relief will be assessed at each blood draw (see attached surveys). If a collection interval is not met there will be no draw retroactively. Participants will be assessed for AE throughout procedures and prior to leaving the visit.

Inclusion/Exclusion Criteria

Aim 1: Adults aged 21 and older who reside in an Ohio Appalachian county and smoke at least 5 cigarettes per day will be considered for this project. Smokers who use other tobacco products (e.g., SLT, electronic cigarettes) > 10 days a month will be ineligible because our goal is to characterize the abuse liability of NPs among those who exclusively or primarily smoke cigarettes.

Inclusion	**Exclusion**
Age 21 years or older	Use tobacco products other than cigarettes >10 days per month.
Reside in an Ohio Appalachian county or surrounding rural area	Use NP in the past 3 months
Willing to complete study procedures, including abstaining from all tobacco,	Unstable or significant psychiatric conditions (past and stable conditions will be allowed)

nicotine, and marijuana for 12 hours before clinic visits	
Ability to read and speak English	Pregnant, planning to become pregnant, or breastfeeding
Smoke at least 5 cigarettes per day for the past 30 days	History of cardiac event or distress within the past 3 months
	Currently attempting to quit all tobacco use
	Self-reported diagnosis of lung disease including asthma (if uncontrolled or worse than usual), cystic fibrosis, or chronic obstructive pulmonary disease

Aim 2: Adults aged 21 and older who reside in any Ohio county and smoke at least 5 cigarettes per day will be considered for this project. Smokers who use other tobacco products (e.g., SLT, electronic cigarettes) > 10 days a month will be ineligible because our goal is to characterize the abuse liability of NPs among those who exclusively or primarily smoke cigarettes.

Inclusion	**Exclusion**
Age 21 years or older	Use tobacco products other than cigarettes >10 days per month.
Willing to complete study procedures, including abstaining from all tobacco, nicotine, and marijuana for 12 hours before clinic visits	Use NP in the past 3 months
Ability to read and speak English	Unstable or significant psychiatric conditions (past and stable conditions will be allowed)
Smoke at least 5 cigarettes per day for the past 30 days	Pregnant, planning to become pregnant, or breastfeeding
	History of cardiac event or distress within the past 3 months
	Currently attempting to quit all tobacco use

3. Study Procedures

Clinic Visits

Informed consent

The participant will arrive at the CTR and meet a member of the research staff in the lobby. The research staff member will escort the subject to a private lab room and review the informed consent form (including a description of the nature, purpose, risks, and benefits of the study). The subject will receive an oral and written explanation of the study. The voluntary nature of the study and the participant's right to withdraw at any time will be stressed during the consent process; a copy of the informed consent will be provided to the participant either electronically or physically at the time of consent for them to keep. Informed consent will be collected by IRB-approved study personnel and stored electronically in the secure database, REDCap.

Recruitment scripts and materials, consent forms, and all study procedures will be approved by the OSU Institutional Review Board. All participants will provide written consent before any study procedures are performed.

Randomization

After participants consent to the study, their visit order will be randomized. Randomization will be counterbalanced and cannot be changed once it is completed. Randomization in Aim 1 involves the 3mg, 6mg, or regular brand of cigarettes while Randomization in Aim 2 involves the 3mg tobacco-derived NP and 2 synthetic NPs.

Obtain baseline exhaled CO test

Participants will need to abstain from tobacco and nicotine products for ≥12 hours prior to their study visit. To check for abstinence from tobacco, participants will perform exhaled carbon monoxide testing (eCO<10ppm) and confirm via self-report that they have not used any other nicotine products over the last 12 hours.

Pregnancy Test

All subjects capable of becoming pregnant will need to take and produce a negative pregnancy test in order to proceed further.

Pre-intervention questionnaire to be administered

This questionnaire will assess sociodemographics, tobacco use history, NP use history, and nicotine dependence. These questionnaires will be administered during Visit 1.

IV line insertion

Because blood draws will occur at set intervals, an IV line will be inserted by a trained staff nurse.

Blood draw to obtain baseline plasma nicotine levels

Next, participants will be reminded that in addition to the exhaled CO test, their abstinence will be confirmed at the time of visit via blood plasma nicotine analysis. 3 mL venous blood sample will be collected for later analysis to confirm abstinence. This blood draw will also be used to establish baseline plasma nicotine levels to estimate total nicotine delivery.

Administer intervention

Aim 1: The participant will receive a 3mg NP, 6mg NP, or be asked to smoke one cigarette of their usual brand depending on the randomization assignment. If smoking a cigarette, participants will be asked to smoke one cigarette following a standardized puffing protocol: they will take one puff every 30 seconds for 5 minutes. If using an NP, participants will be asked to place the pouch between their upper lip and gum and leave it in place for 30 minutes.

Aim 2: The participant will receive a 3mg tobacco-derived NP or a 3mg synthetic NP on randomization assignment. Participants will be asked to place the pouch between their upper lip and gum and leave it in place for 30 minutes.

Peri-intervention questionnaire to be administered
The QSU and MNWS surveys will be administered while at each blood draw interval of 0, 5, 15, 30, 60, and 90 minutes.

Post-intervention questionnaire to be administered
Measures of product appeal and behavioral intentions will be assessed after the participant has the cigarette or NP (Aim 1) or the tobacco-derived vs. synthetic NP (Aim 2).

Schedule return visit and provide gift card for participation
Schedule return visit per subject and interviewer availability that is >2 days after the current visit. Provide $100 via Clincard for their participation out of the up to $350 possible. If it is their last visit has been completed within 1 month from consent, they will receive $150 during their last visit.

Post-Enrollment Survey
6 months after enrolling, participants from Aims 1 and 2 will be recontacted via phone, text, and email for the opportunity to participate in a short online REDCap survey. Participants will complete a short consent addendum and respond to survey questions regarding their current tobacco product use and opinions surrounding nicotine pouches. For their time, they will receive a $10 Amazon gift code.

Procedure Manual
Study procedures, including conducting pregnancy tests, blood draws, blood processing and analysis, gift card administration, and other procedures will be thoroughly explained in the study procedure manual.

4. Study Administration
Randomization, Blinding, and Unblinding
Participants will be randomized within the secure database, REDCap. The randomization piece involves at which of the 3 visits they are to use each product (Aim 1: 3mg NP, 6mg NP, or their own usual brand cigarette and Aim 2: the tobacco-derived 3mg tobacco-derived NP or the 3mg synthetic pouches). Participants will be blinded during study visits and at the end of their third visit will be informed which product they had at each visit.

Study Timelines, Number of Sites, and Enrollment
Participant Timeline
There will be a total of 3 study visits and 1 online survey opportunity 6 months after the completion of the final study visit. The study timeline for each participant will vary. Clinic visits can be completed in as little as a week and a half or as long as 2 months, but will ideally be completed within 3 week’s timeframe for retention and administrative purposes. The study visits will take approximately 3 hours each. The online survey will take approximately 10 minutes to complete and will be offered 6 months after completing the final visit.

Duration of Study
We anticipate the clinical trial to take six months to complete. After that, we anticipate that it will take 1-1.5 years to clean and analyze data and disseminate results.

Total Number of Study Sites
All recruitment and enrollment activities will be completed within the CTR.

Total Number of Subjects Projected
55 subjects will be enrolled and each subject must meet I/E criteria.

Data Collection and Management
Data will be collected and stored electronically in the secure database, REDCap. Data will only be accessible to approved study personnel and will be secured through multiple firewalls. Subjects' first and last names will be deidentified and not linked with the data. The consent forms with first and last names will be databased electronically in REDCap but will not be downloaded with any study data.

Subject Completion, Withdrawal, and Early Termination
Participants will be invited to complete 3 study visits (i.e., participants cannot participate in both Aim 1 and Aim 2) and a supplemental, online survey opportunity to be completed once 6 months after the third clinic visit. The participant timeline will be complete once the 3 study visits are complete. Participants have the option to withdraw at any point by expressing their desire to withdraw to study staff orally or in writing. Study staff will complete a Withdrawal form to document this event. If at any point a participant becomes unable to complete study tasks per protocol (e.g., repeated violations of nicotine abstinence; inconsistent responses reported on questionnaires; showing up to a clinic visit impaired; injury, illness, or medications that impair ability to accurately complete study measures; or inappropriate behavior toward study staff), Dr. Keller-Hamilton reserves the right to ET a participant.

Informed Consent Process
Informed consent will be collected in person by a trained study staff member at the beginning of the initial study visit. Signatures will be documented electronically in REDCap and subjects will be offered an email or printed copy of the consent for their records.

For the 6-month follow on survey, an online consent addendum will be completed prior to the online survey. Signatures will not be collected for the consent addendum and instead the online framework of clicking "next page" will suffice.

Payment to Subjects
Participant compensation will be administered in two tiers: clinic visits and completion bonus.

Aim 1: For each clinic visit, subjects will receive $150. If participants complete all three visits within a month, they will receive a $50 bonus for their participation. Participants could earn up to $500 for their participation. Compensation will be offered in the form of Clincard.

Aim 2: For each clinic visit, subjects will receive $100. If participants complete all three visits within a month, they will receive a $50 bonus for their participation. Participants could earn up to $350 for their participation. Compensation will be offered in the form of Clincard.

If any part of the visit is not possible to complete, participants will be given $50 to thank them for their time.

Aims 1 & 2: 6 months after the final visit is complete, participants from Aim 1 and 2 will be offered participation in a short, 10-minute online survey via email. For their time, participants will receive a $10 Amazon gift code within 2 business days via email.

Confidentiality

Confidentiality will be maintained by all study staff along with the use of a secure study database.

All lab personnel and study staff will complete HIPAA and CITI trainings, human subjects protection training, responsible conduct of research training, and good clinical practices training. Phone scripts will be developed to ensure the subject is in an isolated environment where they are comfortable sharing personal information during the phone screen. During the study visit, participants will be taken to a private lab environment.

The secure databasing platform, REDCap, will store participant data. A subject ID will be assigned to each participant in order to deidentify study data. Multiple levels of security clearance are required before entering the REDCap system and only approved study personnel will have access to this data.

Compliance Statement

Research will be conducted in accordance with CTR policies and IRB regulations. Questions will be directed to OSU IRB representatives and S/AEs will be reported per IRB policy.

Statistical Considerations

Data will be summarized descriptively. For hypothesis testing, we will use linear or logistic mixed effects regression models (with a random subject effect) to assess the main effects of product on plasma nicotine delivery, subjective effects, and behavioral intentions. Model assumptions will be checked, and variables will be transformed as needed. Missing data will not be imputed as likelihood-based linear mixed models will yield valid inference under missing at random assumptions. Models will control for age, sex, and other tobacco use if these features are not balanced by randomization. The same analysis strategy will be used for both aims. We calculated power for Aim 1 based on a repeated measures ANOVA comparing mean total nicotine delivery and maximum plasma nicotine concentration across 3 conditions; existing literature on differences in nicotine delivery across SLT products, including NPs, facilitates the use of this outcome for a power analysis.[9] With a total sample size of only 20 participants and a Bonferroni-adjusted alpha of 0.017, we would have 84% power to detect a mean difference in total nicotine delivery of 25.7 ng/mL and 99% power to detect a mean difference of maximum nicotine concentration of 7.0 ng/mL between products.[9] To account for attrition and the potential need for a larger sample size to detect differences in more subjective outcomes, we will recruit a

sample of 40 participants. For Aim 2, there are no known data to estimate effect sizes and thus to conduct power analyses. The sample size of 15 participants is intended to provide these data for future research.

5. Safety Management, Risks, and Benefits

Safety Management

Clinical Adverse Events

Clinical AE will be assessed by study staff at each study visit via participant self-report and managed immediately. Clinical AE may be related to nicotine overdose or the blood draw. Signs of nicotine overdose include nausea, vomiting, headache, presyncope, tachycardia, and disrupted sleep. With the blood draw, there is a slight risk of bruising, discomfort, and infection with blood draw. Study staff will be trained to recognize these signs and subjects will be encouraged throughout the visit to self-report any AE. In the event of a medical emergency, study staff will be advised to call 911 on the subject's behalf.

AE Reporting

All adverse events will be reported to the OSU IRB. We will monitor for risks associated with smoking and nicotine pouch use by screening participants for general medical precautions (pregnancy, cardiovascular disease). Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be discussed immediately between study personnel and Dr. Keller-Hamilton. Dr. Keller-Hamilton will be responsible for completing an Adverse Events Form should an event occur. Dr. Keller-Hamilton will report potential unanticipated problems involving risks to subjects or others (UPIRSOs) to the OSU IRB within 24 hours of having received notice of the event. Dr. Keller-Hamilton will gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the OSU IRB and the Program Officer at NIH. Adverse event reports will be reviewed annually with the OSU IRB to ensure participant safety.

Risks and Benefits to Participation

Risk Assessment

Every attempt will be made to reduce risk to the participant. The research protocol calls for current smokers who do not plan to quit smoking to try a NP at 3mg or 6mg or smoke their regular cigarette brand (Aim 1) or try a 3mg tobacco-derived NP or 3mg synthetic NP (Aim 2) during a supervised study visit. NPs are no more harmful than conventional cigarettes, and there is some evidence that they may offer reduced harm. Questionnaires and exhaled breath collection procedures are all non-invasive and involve minimal risk to study participants. Potential risks are as follows: a) risk of using NPs, b) use of cigarettes (Aim 1 only), c) loss of confidentiality or privacy, d) potential for undermining smoking cessation, and e) slight risk of discomfort, bruising and infection with blood draw.

Potential Benefits of Trial Participation

Participants are not expected to directly gain any benefits from this study. Participants may indirectly consider quitting tobacco products or choosing a harm reduction product as a result of their involvement with this investigation though this is not a study objective. Through their contributions to science, subjects provide insight into a novel tobacco product that has potential to reduce or increase the harm of tobacco use in Appalachia (Aim 1) or Ohio in general. Moreover, data collected will inform public health efforts, policy, and clinical care aimed at reducing tobacco-related disparities in Appalachia.

Risk-Benefit Assessment

While this trial is not without risk, every effort will be taken to reduce risk and undue burden on participants.

Efforts to reduce risk are as follows:

1. Risk of using NP: The risk of side effects and adverse events are very low. Whether using tobacco-derived or synthetic nicotine, these products are sold online, and at specialty stores and convenience stores nationwide, without a prescription. Nevertheless, all participants will be screened for general medical precautions (pregnancy, cardiovascular disease) and monitored for adverse events during the study period. Study personnel will assess for adverse events via self-report at all follow-up visits. Subjects will also be provided a study phone line to report an adverse event between follow-up visits. Any serious adverse events will be reported to the PI and then to the OSU IRB and potentially to the NIH. We will withdraw participants who have a serious adverse event, or become pregnant or begin to breastfeed. The most likely adverse (potential for nicotine overdose) event is anticipated to be rare (<5% in our previous studies) and mild (nausea, headache, disrupted sleep) event will be handled quickly (i.e., advice to participant to reduce or stop NP use). Our on-site research nurse will also be available to escalate issues as needed and to handle any questions regarding reported adverse events. Lab studies of toxin exposure suggest that NPs incur no greater risk to health than do conventional cigarettes. Moreover, these are all over the counter products and are not significantly different from what the participant typically uses.
2. Loss of Confidentiality and Privacy: Confidentiality will be maintained by numerically coding all data, disguising identifying information, and keeping data locked in file drawers or in a secure, password protected database. All biospecimen samples are kept in a locked freezer and also will be deidentified. Names of participants will be kept separate from participant data. Only study research personnel and the PI will have the information that connects participants' names and ID numbers. All electronic data will be numerically coded and stored in a password-protected database, on a password-protected computer in a secure research space. Participant information will be accessible only to research staff, who are pledged to confidentiality and have completed training in the ethical conduct of research (i.e., both HIPAA and CITI trainings). Identifying information will not be reported in any publication.
3. Potential for Undermining Cessation: The study sample is comprised of smokers with no plan to quit in the next three months. Therefore, we are not asking smokers who want to quit to continue smoking. The PI will be available for any questions that participants may have about NPs, smoking, or smoking cessation. It is important to note that the use of NPs incurs no greater harm than if the participant decided on

his/her own to use the product. Among those screened and ineligible/uninterested, referral resources for smoking cessation will be provided for those who inquire. Among study participants, information on cessation resources will be provided at the final visit and if at any time during the study participants are interested in smoking cessation services, a list of smoking cessation resources will be provided.

4. Slight risk of bruising, discomfort and infection with blood draw: Blood will be collected by trained research staff. Sterile instruments will be used and for blood draws, the participants skin will be cleaned with an alcohol wipe at the venipuncture site.

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