University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

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Study Title: Comparative Abuse Liability of Cigarettes, E-cigarettes, and Heat-not-burn devices among African American and White Smokers

Co- Investigator(s): Eleanor Leavens, PhD; Matt Mayo, PhD; Matthias Salathe, MD

I. Purpose, Background and Rationale

A. Aim and Hypotheses

1. Use of electronic cigarette (e-cigarette) and heat-not-burn (HNB) products is continuing to proliferate in the US. In fact, e-cigarette use is expected to surpass combustible cigarette smoking rates in the next two years. The US FDA has regulatory authority to set appropriate product standards for e-cigarettes and heat-not-burn products with the goal of maximizing public health. Initial data suggest that these products present reduced harm compared to combustible cigarette smoking, but the comparative abuse liability and interest in use by smokers, particularly as a function of product flavor, remains largely unknown. These questions are critical in helping the FDA impose meaningful and effective regulations on these products. African American (AA) smokers are showing increased interest in these new and emerging products. Research suggests AA smokers take larger puffs and inhale more deeply than whites. Therefore, data are needed to understand if AA smokers will also use e-cigarettes and HNB devices in such a way that could inadvertently increase harm in the long run. Additionally, research is urgently needed to understand whether these products (if shown to be less harmful than cigarettes), would be an acceptable alternative to traditional smoking and how product flavor (tobacco vs. menthol) impacts use patterns and preference. The current study is not a cessation study and does not aim to induce long-term uptake of the study products. The objective of the study is to test the acute pharmacokinetic profile of these products during a 65-minute use period with each product across three to four study visits.
2. Aim 1: Understand the abuse liability of heat-not-burn devices, e-cigarettes, and combustible cigarettes in terms of nicotine delivery, puff patterns (topography), and reductions in nicotine withdrawal/craving. *H1:* Combustible cigarettes will show the fastest and greatest nicotine delivery, followed by e-cigarettes, and heat-not-burn devices. *H2:* Topography measures will be greatest for cigarettes, followed by e-cigarettes, and heat-not-burn devices. *H3:* Use of cigarettes will be associated with the greatest reduction in symptoms of nicotine withdrawal and craving.

   Aim 2: Examine resultant toxicant exposure of heat-not-burn devices, e-cigarettes, and combustible cigarettes. *H1:* Exhaled carbon monoxide will be greatest for cigarettes, followed, by heat-not-burn devices and e-cigarettes (no exposure).

Aim 3: Understand the comparative acceptability of tobacco and menthol flavored e-cigarettes among menthol cigarette smokers. H1: Menthol cigarette smokers will show increased topography measures when using the menthol (vs. tobacco) flavored e-cigarette. H2: Menthol cigarette smokers will show increased acceptability and more positive subjective effects when using the menthol (vs. tobacco) flavored e-cigarette.

Exploratory Aim: Understand differences in abuse liability of e-cigarettes, HNB products, and cigarettes as measured behaviorally in a concurrent choice task.

B. Background and Significance

1. Study Significance: Electronic cigarettes (e-cigarettes) and heat-not-burn (HNB) devices have been introduced to the US market in the past 15 years. The US Food and Drug Administration (FDA) is tasked with regulating these emerging products in order to maximize public health. To do this, data are needed regarding product effects including abuse liability (nicotine delivery, addiction potential, and reductions in nicotine withdrawal/craving), product demand, and resultant toxicant exposure. Further, research suggests that these products present reduced harm to the user compared to combustible cigarettes. If this is continually shown to be the case, they may be a less harmful alternative to smoking combustible cigarettes. However, it remains unclear whether they are an acceptable alternative to smokers and whether smokers would choose to use them in place of combustible cigarettes, particularly as a function of flavor (menthol vs. tobacco). Moreover, as more smokers transition to these new and emerging products, it is important to understand how underserved populations will use these products. African American (AA) smokers bear a disproportionate burden of smoking-related diseases and represent an understudied population with a propensity to use products in a way that is different compared to the majority population. AA smokers take larger puffs and inhale more intensely on cigarettes than whites. Therefore, data are needed specific to this population to understand how to maximize public health while avoiding harm to underserved populations, such as AA smokers. The long-term goal of this research is to provide data urgently needed by the public health community and policy makers in order to inform regulatory decisions and maximize public health.
2. Overall Literature Review: The current study will utilize a nicotine salt-based e-cigarette from JUUL. Research from JUUL shows that it can deliver cigarette-like levels of nicotine to the user. [1] One independent study showed that JUUL delivered a higher and faster boost in nicotine compared to other e-cigarette devices and showed that the boost and rate of nicotine deliver was comparable to smoking one cigarette when used by established e-cigarette users.[2] One recent study reports on nicotine delivery among smokers and indicates that JUUL approached but did not reach cigarette-like levels of nicotine delivery.[3] Unpublished data from our laboratory suggest that some smokers are able to effectively extract nicotine from JUUL while others may necessitate significant practice in order to achieve cigarette-like serum nicotine levels.[4] In regards to HNB, we will be using the IQOS device created by Philip Morris International (PMI). Until recently, the only data on the abuse liability and nicotine delivery of this product were from PMI. To our knowledge, only one recently published independent study has been conducted and showed that while IQOS significantly increased nicotine levels

following the 10-puff PK assessment and ad lib use, it did not reach cigarette-like levels of nicotine delivery.[3] Data from PMI on the pharmacokinetics (PK) of IQOS suggest that the device is capable of delivering cigarette-like levels of nicotine in a regimented PK study as well as when users engage in ad lib smoking.[5,6] However, we are unaware of any independent studies comparing the IQOS HNB product, popular e-cigarettes, and combustible cigarettes in terms of nicotine deliver, overall abuse liability, or acceptability for substitution. Moreover, we are unaware of any studies examining these concepts in AA smokers, a population particularly vulnerable to tobacco-related harms.

3. Detailed review:

Does brief exposure to e-cigarettes and HNB devices increase risk to smokers?

- No, there is no evidence to suggest that brief use of e-cigarette or HNB products increases risk to current cigarette smokers above that provided by cigarettes alone. Lab studies of toxin exposure suggest that e-cigarettes incur no greater risk to health than do conventional cigarettes.[7-9] Indeed, e-cigarettes generally show lower levels of harmful and potentially harmful constituents.[7-9] The evidence is so strong regarding the reduced harm of e-cigarettes compared to cigarettes, that the National Academies of Sciences, Engineering, and Medicine has concluded that there is "conclusive evidence" that e-cigarettes are associated with reduced harm compared to cigarettes.[8] To date, e-cigarette studies discussing adverse events report mild and tolerable side effects that generally resolved completely over time with continued use; the most predominant of which were mouth/throat irritation, cough, and headache.[10-12] In four randomized clinical trials, no serious adverse events were reported and the e-cigarette group and the nicotine patch group had comparable levels of adverse events in two studies.[13] The most common were mouth irritation, throat irritation, dry cough and headache.[13] Fewer studies exist on HNB products but those that do, mimic results from studies on e-cigarettes and show that HNB products have lower toxicant levels compared to combustible cigarettes and have lower levels of harmful and potentially harmful constituents.[14] In fact, studies in which smokers are asked to switch to exclusive HNB use, levels of harmful and potentially harmful constituents approach those observed in non-smokers.[15,16] Similar to the e-cigarette literature, research discussing adverse events with HNB products report no serious adverse events and only mild and tolerable side effects that resolve completely over time. The most common adverse effect was cough.[17]

What are the effects of dual e-cigarette and conventional cigarette use?

- Research shows that when smokers begin using e-cigarettes, they reduce the number of cigarettes they smoke per day and show decreases in tobacco-related toxins.[7-9] In a study conducted by Dr. Nollen and her team,[18] smokers were asked to completely substitute with e-cigarettes. Approximately 30% were successful in completely substituting.[18] Moreover, those that did not successfully substitute but instead used both cigarettes and e-cigarettes, significantly reduced their cigarettes per day and showed significant reductions in NNAL, a potent lung carcinogen at 6-week follow-up.[19] While those that switch to these products and those that go on to dual use them show reductions in harm, cigarette smokers

continue smoking at their usual rate and show no reductions in toxicant exposure.[18,19]

What are the effects of dual HNB and conventional cigarette use?

- Less information is known regarding dual HNB and conventional cigarette use because the product has only been on the US market for a short time. However, the existing studies show that when randomized to switch completely to HNB products, 64% switched completely. Moreover, users' levels of NNAL dropped significantly from baseline to follow-up and were significantly lower than NNAL levels in the traditional cigarette group at follow-up.[20] While our study is not a switching or cessation trial, these data suggest that brief use of HNB devices by current smoker swill not increase their harm. It is also unlikely that they will become dual users of HNB products as this has not been documented in the literature.

Does use of e-cigarettes and HNB devices increase conventional cigarette smoking?

- No, e-cigarette and HNB devices do not increase conventional cigarette smoking. As mentioned above, studies conducted by our team show that when provided an e-cigarette, users reduce their cigarette smoking.[18,19] While the HNB literature remains in its infancy, no studies suggest that brief exposure to HNB products increase cigarette smoking.

Is the proposed pharmacokinetic evaluation method common?

- Yes, this method of evaluation is the gold standard for evaluating nicotine delivery and abuse liability.[3,21-27] In addition, studies on relatively newer products almost always recruit smokers because cigarette smoking is the most harmful form of tobacco use in the world. Therefore, it is generally agreed that inviting smokers to use a product with potentially reduced harm for a brief period of time incurs no elevated risk to the participant. To date, this method has been successfully applied to assess e-cigarettes,[3,21-24] HNB products,[3] and waterpipes.[25-27] In fact, a recent publication mimicked this study almost exactly but with white smokers and was published in the highest impact journal in the field of tobacco regulatory science.[3] Researchers on this team have been PI and co-I on five such pharmacokinetic studies.[4,23,25-27]

C. Rationale

1. Industry-funded studies suggest that HNB devices and popular e-cigarettes can deliver cigarette-like levels of nicotine and therefore have comparable abuse liability profiles to combustible cigarettes. If this is the case and research continues to show that these products expose users to less harm compared to traditional cigarettes, they may be an acceptable product for use by current smokers who are unwilling or unable to quite to reduce tobacco-related harm. However, industry-funded studies are open to bias and therefore independent studies are urgently needed to inform appropriate regulations.
2. The current study will provide objective data on the nicotine delivery and overall abuse liability (craving, reductions in nicotine-related withdrawal symptoms), and acceptability of emerging and popular products (HNB and e-cigarettes) among AA smokers, a population particularly vulnerable to tobacco-related harms and who has been underrepresented to date in data aimed at informing regulations to improve public health. Moreover, we will investigate how flavors in e-cigarettes impact product acceptability and abuse liability (i.e., interest in future use, puff patterns/topography, subjective

experience) among menthol cigarette smokers. These data will be used by the FDA to inform appropriate regulation of these products.

3. Tobacco remains the leading cause of preventable death in the US and each year close to half a million people die due to tobacco-related diseases. Therefore, for smokers that are unable or unwilling to quit, products such as e-cigarettes and HNB devices may present less harm and improve public health.

II. Research Plan and Design

A. Study Objectives: The objective of this study is to understand the abuse liability and resultant toxicant exposure of new and emerging tobacco products in comparison to smokers' usual brand cigarette and to further understand how flavors in e-cigarette products impact abuse liability among menthol cigarette smokers. The current study is not a cessation study and does not aim to induce long-term uptake of the study products. The objective of the study is to test the acute pharmacokinetic profile and acceptability of these products during a 65-minute use period with each product across three to four study visits. African American and white smokers (N = 20) will be recruited and complete three to four in-laboratory sessions in a randomized crossover design.

B. Study Type and Design: The proposed study is a randomized crossover trial. Current smokers will be randomized to session order and complete a standardized 10-puff bout (5 minutes) followed by a 60-minute ad libitum session with each product (usual brand cigarette, e-cigarette, heat-not-burn). Throughout each visit, blood will be collected for nicotine analysis via an IV catheter placed in the patient's arm. Blood samples will be aliquoted into two separate vials. One will be analyzed for the current study and one will be placed in a biospecimen repository if participant provides consent for biorepository. Puff topography will be collected passively throughout the session to measure puffing patterns. Participants will complete self-report measures of nicotine withdrawal and craving. Finally, breath samples will be collected to measure changes in exhaled carbon monoxide, a potent lung toxicant, pre- and post-product use. At the final visit, participants will complete a behavioral economics concurrent choice task (see below for description) to behaviorally measure their decisions regarding use of e-cigarettes or HNB products in place of cigarettes. Finally, participants will be contacted by phone 6 months following the conclusion of visit 3 (or study discontinuation) to complete a phone survey. The objective of this survey is to assess for ongoing use of study products and is part of safety monitoring. We have no hypotheses related to the follow-up.

Participants who report typically smoking menthol cigarettes will be invited to complete a fourth session. Participants will undergo overnight tobacco/nicotine abstinence before the visit (eCO$\leq$12ppm). Participants will then be randomized 1:1 to e-cigarette flavor order (tobacco e-cigarette, menthol e-cigarette) and will complete sessions in a counterbalanced fashion to control for order effects. They will complete a 30-minute ad libitum session with the first product, based on randomization, followed by a 1.5-hour standard washout period, followed by a 30-minute ad libitum vaping session with the second product (menthol or tobacco flavor). Throughout each session, puff topography will be measured via a pressure sensor attached to the e-cigarette device. Participants will complete self-report measures of smoking urges and withdrawal symptoms pre- and post-

vaping session. In addition, they will complete measures of subjective vaping experience, perceptions of flavor, product demand, and intentions for future use.

C. Sample size, statistical methods, and power calculation

1. 20 eligible AA and white smokers will be randomized. We will use a 1:1 fashion randomization to product order (combustible cigarette, e-cigarette, heat-not-burn device vs. combustible cigarette, heat-not-burn device, e-cigarette). Randomization will be determined by computer-generated random numbers. Randomization assignments will be placed in sealed envelopes with sequential study ID numbers. After baseline data collection has been completed, the research assistant will select the sequential study ID number to determine the randomization assignment
2. No blinding is involved in the first three study visits. For participants who complete the fourth visit (flavor assessment), participants and research assistants that interact with participants will be blind to flavor (double blind design).
3. Due to the pilot nature of the current study, a primary aim of the study is to collect data for power calculations for a fully powered trial. Therefore, formal power calculations were not conducted. ANOVAs will be conducted to detect within-subject differences between products for all outcomes. A Bonferroni correction will be applied to adjust for multiple comparisons. A paired samples t-test will be conducted to detect differences in outcomes in the e-cigarette flavor assessment.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

Participants will be AA and white adult smokers ≥21 years old. The study will be open to both men and women. We have chosen to focus on AA because their unique smoking profile places them at potentially greater risk for tobacco-related disease and death and because AA smokers are understudied in terms of the potential differential effect of tobacco-related policy among this population. Women who are pregnant, plan to become pregnant, or are breastfeeding will be excluded from the study because tobacco products will be provided and smoking is associated with low birth weight and premature labor. Children and those <21 years old will be excluded because the minimum age for purchasing tobacco products is 21 years old.

1. Inclusion criteria: Non-Hispanic African American or white/Caucasian, ≥21 years old, smoke 5-30 cigarettes per day, daily cigarette smoker, smoked at current rate for at least 6 months, interested in trying e-cigarettes and HNB products, not interested in or unable/unwilling to quit cigarette smoking, willing to complete three in-person study visits, willing to have IV catheter placed.
2. Exclusion criteria: Interested in quitting cigarettes in the next 30 days, use of smoking cessation pharmacotherapy in the past 30 days, use of non-cigarette tobacco products in the past 30 days, use of e-cigarettes >5x in lifetime, use of e-cigarettes ≥4 of the past 30 days use of HNB products >5x in lifetime, use of HNB products ≥4 of the past 30 days, weight < 110 lbs, uncontrolled hypertension (systolic BP ≥ 180 or diastolic BP ≥ 105), pregnant, plans to become pregnant, or breastfeeding, live >10 miles from study site (Fairway CRU), current enrollment is a research study or program that aims to alter tobacco use.
3. Withdrawal/Termination criteria: Participants will be instructed to practice with (and attempt to switch to) each device prior to attending study visits 2 and 3. Participants may be removed from the study if they fail to complete

sufficient practice prior to each study visit. Additionally, participants will present to the lab nicotine deprived (12 hours abstinent) for study visits 1, 2, and 3. If participants present to study visit 1 and eCO is greater than 12 ppm or they report other nicotine use two times, they will be removed from the study.

4. Participants will not be allowed to participate in another research study that aims to alter their tobacco use during this research study.

A. **E. Specific methods and techniques used throughout the study**

1. Laboratory tests: Throughout each visit, blood will be collected for nicotine analysis via an IV catheter placed in the patient's arm. Blood draws will occur during the PK phase of each visit and will be taken at baseline (0 minutes), 5 minutes, 7 minutes, 15 minutes, and post-ad lib portion (may vary by participant depending on how long they choose to use the product). No more than 7 mL of blood will be drawn per draw (≤35 mL per visit). Blood will be processed and analyzed for nicotine and cotinine levels. If consent is provided for banking, samples will be banked for possible future analysis.
2. Study Procedures:
    a. **Initial screening:** The initial screening will review inclusion/exclusion criteria. Those eligible will be scheduled to completely visit within 14 days.
    b. **Visit one:** At visit one, participants will be re-screened according to inclusion/exclusion criteria. They will be instructed to remain nicotine abstinent for 12 hours prior to the visit. Participants will complete carbon monoxide (CO) measurement to confirm abstinence (CO ≤ 12 ppm). CO is collected by a simple, non-invasive breath test that involves the participant holding their breath for ~15 seconds and then exhaling into a straw connected to the CO monitor. Participants will be provided with an overview of the study, will provide informed consent, and complete baseline self-report measures. Participants will then complete the PK phase of the study. Participants will have an intravenous catheter placed in their arm. They will complete a 10-puff standardized puffing bout followed by a 60-minute ad-lib smoking session with their usual brand cigarette. Specifically, a research assistant with a stopwatch will instruct the participant to take a puff every 30 seconds, resulting in 10 puffs over 5 minutes. Throughout the session, puff topography will be measured via a pressure sensor attached to the device/product. This will not require anything additional of the participant. Blood draws will occur during the 10-puff bout at -5, 5, 7, 15, and at the end of the ad-lib smoking period (~60 minutes after the 10-puff bout). Following the smoking period, the participant will be instructed to make notes regarding their preferences related to the product (e.g., liking, satisfaction, craving, intentions/willingness for future use). Participants will complete self-report measures of nicotine craving and withdrawal at each blood draw during the 10-puff bout and every 10 minutes throughout the ad-lib smoking period. At the end of the session, participants will complete a measure of product liking/evaluation. At the end of visit one, participants will be randomized to product order (e-cigarettes followed by HNB device vs. HNB device followed by e-cigarette). Participants will be shown how to use the device, puff on it, charge it, replace the pod/heat stick. Participants will be compensated $50 for this visit. In

addition, participants will be asked to bring an unopened back of their usual brand cigarettes to this visit. They will be compensated an additional $6 for this, bringing their total compensation to $56 for this visit. We anticipate the visit to last no more than 3 hours.

c. **Between visits one and two:** Participants will be provided with the product to be used at the next visit (determined by randomization completed at the end of visit one) and asked to take it home for 48 hours (+3 days) and instructed to, at minimum, practice using it 2-3 times per day between visits. However, they will be encouraged to full substitute the study product for their cigarettes to ensure they conduct sufficient practice. They will be provided with e-liquid or heat sticks and the device for practice. Participants will complete and return a practice log at the following visit.
d. **Visit two:** Aside from the product being used, visit two will closely mirror visit one. Participants will complete baseline self-report measures regarding their practice period (product liking/evaluation and preferences). Participants will again complete CO measurement to confirm tobacco/nicotine abstinence. They will complete a PK and ad-lib session identical to visit one. At the end of the session, they will be oriented to the final device and again instructed to practice with (and attempt to fully substitute) it at home. Participants will be compensated $75 for this visit. We anticipate the visit to last no more than 2.5 hours.
e. **Between visits two and three:** Participants will be provided with the product to be used at the next visit (determined by randomization completed at the end of visit one) and asked to take it home for 48 hours (+3 days) and instructed to, at minimum, practice using it 2-3 times per day between visits. However, they will be encouraged to full substitute the study product for their cigarettes to ensure they conduct sufficient practice. They will be provided with e-liquid or heat sticks and the device for practice. Participants will complete and return a practice log at the following visit.
f. **Visit three:** Aside from the product being used, the first portion of visit three will closely mirror visits one and two. Participants will complete baseline self-report measures regarding their practice period (product liking/evaluation and preferences). Participants will again complete CO measurement to confirm tobacco/nicotine abstinence. They will complete a PK and ad-lib session identical to visits one and two. Following the PK and ad-lib sessions, participants will have a 1.5-hour washout/rest period in order to bring them to a state of nicotine deprivation. During the washout period, participants will be allowed to watch a movie or listen to music. Participants will then complete a concurrent choice task with their usual brand cigarette, e-cigarette, and HNB device. In the task, participants will earn puffs of the various products by clicking a mouse/keyboard a set number of times. The participants will be free to choose how they allocate the puffs between the available products. For each task, participants can earn up to 20 puffs and the task will last up to 1.5 hours. Puff topography will be measured throughout the task. The objective of the task is to behaviorally measure whether or not participants see the e-cigarette and/or HNB device as an acceptable or preferable substitute for their usual brand cigarette. Participants will be compensated $100 for visit

three. In addition, participants will earn up to $50 for completing all study visits (see section III.G.). We anticipate that visit three will last no more than 4.5 hours.

i. **Computer task:** The usual brand cigarette, e-cigarette, and HNB product are all available. Participants will earn puffs of the products by clicking boxes on a computer screen that represent the products. To earn 1 puff of a product, the participant will be instructed that they must click the corresponding box. In order to earn puffs of the e-cigarette or HNB product, they will click the corresponding box 10 times. To test relative demand for their usual brand cigarette, it will be placed on a variable ratio, meaning the number of clicks necessary to earn puffs of the usual brand cigarette will increase with each trial of the task. Once participants earn a puff, they will be given two minutes to have the puff before the next trial begins.

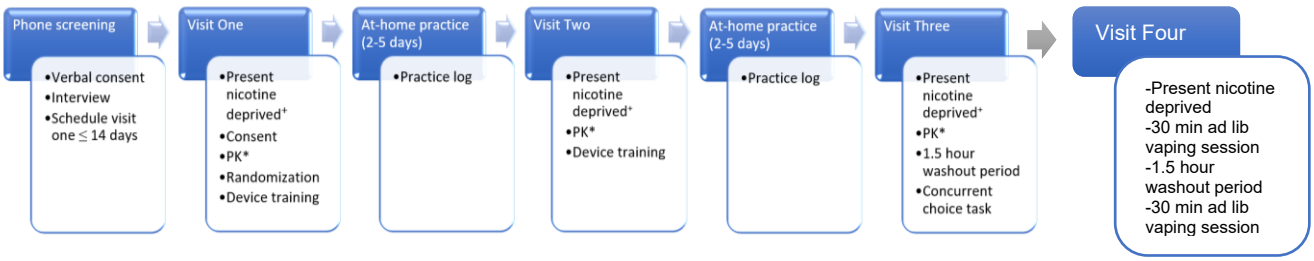
Computer screen simulation for task:

g. Visit four (menthol smokers only): Participants who report typically smoking menthol cigarettes will be invited to complete a fourth session. Participants will undergo overnight tobacco/nicotine abstinence before the visit (eCO≤12ppm). Participants will then be randomized 1:1 to e-cigarette flavor order (tobacco e-cigarette, menthol e-cigarette). They will complete a 30-minute ad libitum session with the first product, based on randomization, followed by a 1.5 hour standard washout period, followed by a 30-minute ad libitum vaping session with the second product. Throughout each session, puff topography will be measured via a pressure sensor attached to the e-cigarette device. Participants will complete self-report measures of smoking urges and withdrawal symptoms pre- and post-vaping session. In addition, they will complete measures of subjective vaping experience, perceptions of flavor, product demand, and intentions for

future use. We anticipate that the session will last ~3 hours. Participants will earn $50 for attending the study visit.

h. **<u>Six-month follow-up:</u>** Six months after completion of visit 3 (or study discontinuation), participants will be contacted by phone to assess ongoing use of study products. Three attempts will be made to contact the participant for this follow-up. If they endorse ongoing use, they will be advised to quit all tobacco use and offered a referral to the Quitline. We anticipate this phone follow-up to last no more than 10 minutes. This follow-up assessment is for safety monitoring only.

3. Due to COVID-19 and the need to keep patients and researchers safe, we will use Zoom, a HIPAA compliant, university approved video conferencing software, during the visit. This will allow the participant to smoke freely (unmasked) while the researcher can watch and communicate with the participant via video conferencing from outside the clinic room. We will utilize Zoom as much as possible and only enter the room when absolutely necessary.
4. All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.
5. Samples will be labeled only with a unique study identification number and only members of the research team will have access to the samples. Samples will be disposed of one month after the final report is sent to the Principal Investigator, unless participants agree to have their samples stored for future testing.
6. Timeline/project flow:



Note. +CO ≤ 12 ppm; *blood draws, topography, self-report measures of craving, withdrawal, and product liking. 6 month follow-up not depicted.

F. Risk/benefit assessment:

1. Physical risk: The potential risks for this study are minimal. There is a slight risk of discomfort, bruising and infection with blood draw. Blood will be drawn by trained research staff. IVs will be placed by an RN or LPN. Sterile instruments will be used and for blood draws, the participants skin will be cleaned with an alcohol wipe at the site of the needle stick. Participants will complete no more than two study visits in a seven-day period.
2. Psychological risk: Risks for participants include those associated with the inconvenience of participation including answering surveys, providing blood samples, and completing multiple visits. To minimize the inconveniences associated with study participation we will review all data collection instruments and study procedures to minimize the number of items in our instruments and improve the accessibility and convenience of our study procedures. We anticipate using several methods to enhance convenience to participants, including providing rideshare services to and from all study visits and offering study visits throughout the day. Another risk is feeling pressured to be in the study, which we will track in order to monitor and will report as

an adverse event. Finally, although very unlikely, some questions may make participants uncomfortable; participants are not required to answer questions they do not wish to.

3. Social risk: None
4. Economic risk: None
5. Potential benefit of participating in the study
    a. There are no direct benefits to participants for participating in this study
    b. The researchers hope that the information gathered from this research may be useful in informing regulations to maximize public health

G. Location where study will be performed: The screener visit will take place at Swope Health Central, 3801 Blue Parkway, in Kansas, Missouri or at the KUMC CRU in Fairway, Kansas based on the preference of each participant. Study visits 1, 2, and 3 will take place at the KUMC CRU in Fairway, Kansas. All data will be directly entered into an electronic data capture system (i.e., RedCap or CRIS), therefore minimizing the use of paper records. If paper records are generated, they will be stored in locked file cabinets. Only study staff will have access to the locked records and the secure online electronic data capture system.

H. Collaboration (with another institution, if applicable): N/A

I. Single IRB Review for a Multi-site study (if applicable): N/A

J. Community-Based Participatory Research (if applicable): N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): Personnel on the project include Nikki L. Nollen (PI), Eleanor L. S. Leavens (co-investigator), Matt Mayo (co-investigator and biostatistician), Matthias Salathe (co-investigator), Tricia Snow (program coordinator director), TBD (GRA), CRU staff
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Eleanor Leavens, Nikki Nollen, Tricia Snow, Matthias Salathe, and GRA
    b. Obtaining informed consent: Eleanor leavens, GRA
    c. Providing on-going information to the study sponsor and the IRB: Eleanor Leavens, Nikki Nollen, Tricia Snow
    d. Maintaining participant's research records: Eleanor Leavens, Nikki Nollen, Tricia Snow, Matt Mayo, GRA
    e. Completing physical examination: N/A
    f. Taking vital signs, height, weight: CRU staff, Eleanor Leavens, GRA, Tricia Snow
    g. Drawing / collecting laboratory specimens: CRU staff
    h. Performing / conducting tests, procedures, interventions, questionnaires: Eleanor Leavens, GRA, Tricia Snow
    i. Completing study data forms: Eleanor Leavens, GRA, Tricia Snow, CRU staff
    j. Managing study database: Matt Mayo, Tricia Snow, Eleanor Leavens, Nikki Nollen

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. The current study does not pose more than minimal risk; however, we are extremely sensitive to the recent cases of acute lung injury associated with e-cigarette products and the CDCs warnings. We continue to closely monitor the situation. To address this concern, we will obtain informed consent, closely monitor AEs and SAEs and promptly report any that occur. Dr. Salathe will provide medical oversight. In addition, we will have firm stopping rules to protect the safety of study participants. Further, we will purchase our supply directly from JUUL and will advise participants to not modify the e-liquid in any way – e.g., adding THC or vitamin E – which has been the case in the majority of reported cases. Altering the e-liquid would be difficult as participants will be provided JUUL pods which are closed systems, not easily tampered with. We also include a 6-month follow-up to assess for any on-going study product use and again offer a referral to the Quitline.
2. We will protect participants and minimize risks by using the strict exclusion criteria and careful monitoring of AEs. AEs will be tracked during regularly scheduled visits (including 6-month phone follow-up) or through spontaneous reports made by participants. Drs. Leavens, Nollen, and Salathe will be made aware of unexpected or serious AEs within 24 hours of the first report by participants; all other AEs will be reviewed weekly by Drs. Leavens Nollen and discussed at regular meetings with Dr. Salathe. SAEs will be reported to the KUMC IRB within 24 hours of first awareness of the event. Unexpected adverse events that are related to the study products will be reported to KUMC IRB within 5 working days of first awareness of the event if the event is not serious and within 24 hours of first awareness if the event is serious. Unexpected adverse events that are unrelated to the study products will be reported to the KUMC HSC during yearly routine event reporting. Dr. Salathe will determine relatedness for each reported AE. SAEs will be defined as any event experienced by a study subject while using the study device that is fatal, life-threatening (subject was at risk of death from the event as it occurred), disabling or incapacitating, requires inpatient hospitalization or prolongs a current hospitalization, or required intervention to prevent permanent impairment or damage.
3. In the case of AEs, participants will be reminded of the voluntary nature of the study and be allowed to discontinue participation without negative consequences. In the case of SAEs related to use of study products, participation will be discontinued.

III. Subject Participation

A. Recruitment:

1. Participants will be recruited through clinic, community-based efforts, and social media platforms. Flyers will be placed around Swope and KUMC for patients to take. We will use the KUMC HERON database and the TMC electronic medical records to identify smokers and will ask their physician to send their patient a letter informing them of the study. We will also use the Frontiers registry to identify adult smokers who have agreed to be contacted for research. We will also use radio ads, word of mouth, and our existing pool of participants from prior studies. We will post the study to the KUMC Intranet list of current studies for KUMC employees. Additionally, participants are currently being screened for other research studies conducted by our team. Those who have completed studies or who are ineligible for other studies being conducted will be informed about the current study and offered the

opportunity to be screened. Recruitment letters, advertisements, and flyers are in the process of being developed. They will be submitted to the IRB for approval before any participants are enrolled.

2. Recruitment methods are described above. Recruitment will be conducted by members of the study team. Recruitment will be overseen by Drs. Nollen and Leavens. Screening will be conducted over the phone.
3. Advertisements and flyers that will be used for recruitment are attached. Advertisements and flyers will be handed out to potential participants by the study team and will be placed in clinics at Swope and KUMC.

B. Screening Interview/questionnaire: The screening will be conducted over the phone. The screening questionnaire will address the general inclusion/exclusion criteria as listed above. Only participants who have expressed interest will be screened. Prior to screening, participants will be given a brief overview of the study and informed that we need to collect some information to learn whether they may be eligible for the research. They will be informed that completion of the screening interview is voluntary, and they can discontinue screening at any time. Participants will be asked to provide verbal consent for screening.

C. Informed consent process and timing of obtaining of consent

1 Consent procedures will be conducted by trained members of the research team. Prior to consent, participants will be provided a detailed and comprehensive overview of study procedures.

2 Individuals interested in the proposed study will meet the research assistant at the Fairway CRU. Each individual will be given a copy of the consent form and as much time as they need to review its contents. After the consent form is read, both the individual and the research assistant will review the consent form together and the potential participant will be encouraged to ask questions. Each individual will be reminded that participation in the study is completely voluntary**.** The consenting process will take place in a private location.

3 We are recruiting otherwise healthy smokers and do not anticipate recruitment of subjects with compromised cognitive abilities and/or decisional impairment. However, if questions regarding a participant's ability to provide informed consent arise, Drs. Nollen and Leavens will determine whether the subject is able to give informed consent.

D. Alternatives to Participation: The alternative to participation is not participating.

E. Costs to Subjects: There are no costs to participants. All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

F. How new information will be conveyed to the study subject and how it will be documented: We have plans to publish data from this study in aggregate but will not provide any individualized feedback to patients.

G. Payment, including a prorated plan for payment: Participants who screen fail at visit one will be compensated $20 and will not be allowed to continue with the study. Eligible participants who complete study procedures will receive $50 for visit one, $75 for visit two, $100 for visit three, and $50 for visit four (if

participant qualifies) in appreciation for their time and participation. Participants may receive an addition $50 at visit three if they attend all visits, return completed practice logs, and have CO ≤ 12 ppm at all visits. For each visit that must be rescheduled due to CO > 12 ppm or an incomplete practice log, participants will have $10 deducted from their bonus. Finally, participants will be provided transportation via a rideshare service to and from each visit.

H. Payment for a research-related injury: N/A

IV. Data Collection and Protection

A. Data Management and Security: Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet. The screening questionnaire and all survey data will be directly entered into RedCap or CRIS and accessible only by study staff. Any paper copies of records will be kept in a locked filing cabinet in offices that are kept locked when unoccupied. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. Because identifiable information will be collected, participant privacy will be maintained throughout the duration of the study by adhering to the regulations set forth by the HIPAA Privacy Rule. More specifically, identifiable information will not be released without written authorization of the participant. Mobile devices will not be used for data collection or storage. Identifiable data will not be sent outside of KUMC.

B. Sample / Specimen Collection: No more than 7 mL of blood will be collected per blood draw (7 mL per draw x 5 draws per visit x 3 visits = 105 mL total during study). All samples will be de-identified and labeled with a study identification number. Blood samples will be aliquoted into two separate vials. One will be analyzed for the current study and one will be placed in a biospecimen repository if participant provides consent for biorepository. Participants will complete no more than two study visits in a seven-day period. Samples will be stored at the Bioanalytical Laboratory at the Fairway Clinical Research Center under the direction of Greg Reed, PhD. Samples will be accessible only to members of the study team. Results from biomarker analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified. Samples will be disposed of one month after the final report is sent out to the Principal Investigator, unless participants agree to have their samples stored for future testing. For participants who agree to future testing, samples will be stored indefinitely.

C. Tissue Banking Considerations: For participants who agree to future testing, samples will be stored indefinitely. New markers of nicotine and carcinogen exposure and genetic differences in nicotine metabolism are being discovered and the stored biological samples would be used for analysis of these new markers. All samples stored for future biomarker analyses will be de-identified and accessible only to members of the study team. Results from these analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified.

D. Procedures to protect subject confidentiality: Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. All biological samples and survey data will be labeled with the study identification number and never with the participants name or other identifiable information. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet and will only be accessible to members of the study team.

E. Quality Assurance / Monitoring: All data will be directly entered into our electronic data capture system (i.e., RedCap or CRIS) that contains edit checks to control the quality and completeness of data entry. Completeness of data entry will be automatically verified before each assessment is completed. The electronic data capture system is behind the KUMC secure firewall with role-based access that is HIPAA and human subjects compliant. There are no plans for ongoing third-party monitoring.

V. Data Analysis and Reporting

A. Statistical and Data Analysis: See section II.C. above for sample size and power calculations. To determine differences on self-report measures between products, an analysis of variance (ANOVA) will be conducted. Differences in nicotine delivery will be compared across products at each timepoint using similar procedures. Mean differences in puff allocation will be investigated for the computer task.

B. Outcome: The primary study endpoint is nicotine delivery. We hypothesize that combustible cigarettes will show the fastest and greatest nicotine delivery, followed by e-cigarettes, and heat-not-burn devices. Further, topography measures will be greatest for cigarettes, followed by e-cigarettes, and heat-not-burn devices. In terms of self report measures of abuse liability, use of cigarettes will be associated with the greatest reduction in symptoms of nicotine withdrawal and craving. Exhaled carbon monoxide will be greatest for cigarettes, followed, by heat-not-burn devices and e-cigarettes (no exposure). The primary endpoint of the computerized concurrent choice task is the proportion of puffs allocated to each product. The third aim is exploratory, and we therefore do not have specific hypotheses related to aim three.

C. Study results to participants: Study results will not be shared with research participants.

D. Publication Plan: We plan to publish results in appropriate tobacco and public health journals such as Addiction, Tobacco Control, Nicotine and Tobacco Research, etc. In addition, results will be presented at regional, national, and international conferences.

APPENDIX I: VULNERABLE POPULATIONS

N/A

VI. Bibliography / References / Literature Cited

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