"Effects of Nicotine Salt Aerosol on Cigarette Smokers"
Institutional Review Board Study Protocol

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Background: Cigarette smoking continues to be the greatest preventable cause of death in the US, responsible for more deaths per year than illegal drugs (including opioids), alcohol, guns, car accidents, and HIV *combined* (Mokdad et al., 2004; Seth et al., 2018; US Department of Health and Human Services, 2014). Despite considerable declines in smoking, projections suggest that over 5 million youth, or 2 out of every 27 children alive in the US today, will die prematurely from cigarette smoking (US Department of Health and Human Services, 2014). Cigarette smoking is a health disparity issue, with higher rates among Native Americans, multiracial individuals, and those with less education and lower income (Wang et al., 2018). The combustible cigarette is an unreasonably dangerous, defective product, killing half of all long-term users (Gray and Boyle, 2000; Peto et al., 1992; Proctor, 2013; Yang, 2018). Most smokers report wanting to quit, but are unable to maintain abstinence (CDC, 2011). Quit rates can be enhanced by Nicotine Replacement Therapies (NRT) and other pharmacotherapies. In clinical trials, NRT performs superior to placebo with quit rates of 18-31% (Fiore et al., 2008). However, among the general population, many do not use NRT. Among those who do, only 5 to 15% are able to quit (Curry et al., 2003), partially because the majority of NRT users discontinue use early, largely due to dissatisfaction with NRT (Fiore et al., 2004; Shiffman et al., 2002; Wiggers et al., 2006). The development of a safe method of nicotine delivery that is appealing to cigarette smokers has potential to be a major public health advancement.

Electronic nicotine delivery systems (ENDS) aerosolize liquid nicotine that the user inhales in a process similar to cigarette smoking. ENDS are considered tobacco products under US law as long as they include plant-derived nicotine and are not marketed with therapeutic intent (Sottera, Inc v. FDA, 627 F.3d 891, DC Cir. 2010). Although many ENDS deliver nicotine, flavor additives, and other potentially addictive or harmful chemicals, they do not burn tobacco, a process that yields an estimated 7000 chemicals, including at least 70 carcinogens (Douglas et al., 2018; US Department of Health and Human Services, 2014). Former smokers who use ENDS rate ENDS as less risky, better tasting, more satisfying, and better at reducing craving, negative affect, and stress than FDA-approved NRT (Harrell et al., 2015). Smokers who switch completely to ENDS substantially reduce their exposure to numerous toxicants and carcinogens present in combustible cigarettes, thus improving their health in the short term (Goniewicz et al., 2014; Harrell et al., 2014). In a 2018 report reviewing the scientific evidence, the National Academies of Sciences Engineering and Medicine (NASEM) determined there is "conclusive evidence that completely substituting e-cigarettes [ENDS] for combustible tobacco cigarettes

reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes (NASEM, 2018)."

From 2015-2017, an ENDS marketed as "Juul" went from being a little-known brand with low sales into being the largest retail ENDS brand in the US, lifting sales of the entire ENDS category (Huang et al., 2018). Juul differs from many other ENDS in the use of nicotine salts (protonated nicotine). Nicotine salts may play an important role in the effects of Juul, but this has not been systematically assessed. Preliminary research on Juul devices suggest they may be safer than other ENDS devices (Reilly et al., 2018), which, as noted previously, appear substantially safer than cigarette smoking (National Academies of Sciences Engineering and Medicine, 2018).

Research questions: Does the use of nicotine salts (protonated nicotine) differ from regular (unprotonated) nicotine or own-brand cigarette in: 1) cigarette craving reduction; 2) withdrawal symptoms reduction; and 3) appeal as measured on a variety of dimensions regularly assessed for tobacco products?

Study design:

Laboratory space: Laboratory space in Williams Hall contains filtration devices to remove any secondhand smoke or aerosol (from cigarettes or ENDS). In consultation with Thomas Eissenberg at Virginia Commonwealth University and S. Doug Martin, Executive Director of Facilities at EVMS, approximately $50,000 was spent designing and equipping these rooms. This laboratory was designed for smoking research and includes a ventilation system so that others are not exposed to second-hand smoke unduly.

Sample size: A total of 30 participants are planned to allow for statistical power to examine differences (Within-Subjects) in the physiological and subjective effects of the products. Using a Repeated Measures Within-Subjects design, this will allow for detection of a large effect size (Cohen, 1992; Faul et al., 2009). We may consent up to 75 participants in order to obtain 30 participants who complete the entire study.

Recruitment: We will recruit current cigarette smokers using a recruitment database submitted separately (PR-2871-EVMS). Potential participants will find this recruitment database via advertising on Craigslist, newspapers, internet forums, flyers in the local area, and local clinics. There is a flyer specifically for this study that will direct individuals to participate in the registry online questionnaire Screening data will be obtained from this online questionnaire. See separate protocol submitted. Screening data will be compared against the inclusion and exclusion criteria listed below to determine if participant is eligible for this study. Eligible participants will be contacted to provide more information about the study. Participants will be told they can smoke as normal for their first visit, but must abstain for 12 hours (typically overnight) before the 3 other visits. Those who meet screening criteria and are still interested in the study will be scheduled to come in for laboratory visits.

Inclusion Criteria: All participants must be healthy (determined by self-report), between the ages of 18-55, willing to provide informed consent, and willing to attend the EVMS lab 4 times and abstain from smoking for 12 hours (typically overnight) for 3 of these visits. Participants must smoke at least 10 cigarettes per day (i.e., be regular cigarette smokers). Self-report of smoking will be bioverified on the initial screening visit.

Exclusion criteria: Individuals will be excluded based on a self-reported history of (1) unstable or significant current medical condition (recent heart attack or other heart conditions including high blood pressure); (2) severe immune system disorders (uncontrolled HIV/AIDS,

unstable multiple sclerosis symptoms), (3) respiratory diseases (exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis) or any medical disorder/medication that may affect participant safety, study outcomes, or biomarker data will be excluded. Individuals who report more than 25 days of alcohol use in the past 30 days or more than 15 days of marijuana use in the past 30 days will be excluded. Individuals with past month use of cocaine, opioids, benzodiazepines, and methamphetamine will be excluded. Participants with current, diagnosed psychiatric conditions will also be excluded. Participants will be excluded for any use of an ENDS product in the past 30 days, or any report of daily use of ENDS for a week or more. Regular use of ENDS is excluded as we are interested in understanding the effect of these liquids on smokers who are relatively naïve to ENDS use so that prior experience does not obscure laboratory experience of use.

Initial laboratory screening visit: Potential participants will be informed prior to this session to provide a list of current prescription medications or bring in their medication bottles in with them to confirm any medications listed on the screening survey. When participants arrive, air filters will be on in the laboratory space in order to encourage familiarity with the noise during laboratory sessions. Potential participants will be provided with a copy of the informed consent document. (See attached.) Research Assistants will review the informed consent document with the potential participant and answer any questions. If still interested, the form will be signed and a copy provided. Next, participants will breathe into a Carbon Monoxide (CO) monitor. (Cigarette smoking involves the inhalation of Carbon Monoxide.) In addition, participants will provide a saliva sample to test for cotinine, a metabolite of nicotine. If participants do not have a CO level of at least 15 ppm and a cotinine test strip level of at least 3 (indicating 100-200 ng/ml cotinine), then they will not be allowed to continue with the study. These results would indicate that they are not regular cigarette smokers. Female participants will also provide a urine sample using the nearby restroom. A pregnancy test strip will be used. If the test does indicate pregnancy, the result will be discussed with the participant and she will be urged to seek prenatal medical care. Information will be provided about where to receive such care (either with their regular physician or at a free clinic). Otherwise, staff will next assess heartrate and blood pressure using an arm blood pressure cuff and a pulse oximotor. Participants will deemed ineligible at screening if their resting heart rate (HR) exceeds 110 beats per minute (bpm), systolic blood pressure (BP) exceeds 140 mm Hg, or diastolic BP exceeds 100 mm Hg. If they do demonstrate eligibility (regular cigarette smoker, not pregnant, acceptable vital signs), they will complete a W9 to facilitate payment processing and complete baseline questionnaires (DemographicPersonalHealthInfor, PennState, Fagerstrom, BaselineExpectancies) on the REDCap system. (See attached document.) Finally, following completion of the baseline questionnaires, the Research Assistant will review with the participant the next 3 scheduled visits and emphasize the need to abstain from smoking and nicotine products for 12 hours (typically overnight) and pass testing before their next visit.

Smoking/"Vaping" Lab Sessions: The sessions will occur no more than 2 days per week and will be separated by at least 48 hours. The approximate total time that participants will be in the laboratory is 12.5 hours (30 minutes for screening and 12 hours for 3 4-hour long sessions). This does not include the 12 hours before each session that we ask participants to abstain from smoking.

Note: Most questionnaires are completed via computer in the laboratory. The only exception for subjects is the glms, administered via pen & paper. EnrollmentInformation, SessionInformationSheet, BiochemicalTestResults, and the SaltStudySessionSheet are completed by Research Staff.

The session will begin with the participants' self-report of their last cigarette, CO expired air testing, and cotinine saliva testing. If the last cigarette smoked was within 12 hours or CO is above 10 ppm, the participant will be told they need to reschedule for another time and must abstain for 12 hours before the next visit. If there are 2 consecutive sessions indicating non-compliance, the participant will be disqualified from the study and paid as outlined in the compensation section. If participant's tobacco abstinence is bioverified, they will begin a 1-hour waiting period to ensure nicotine abstinence. Nicotine abstinence (e.g., ENDS, NRT) unfortunately cannot be bioverified quickly. Blood analyses at VCU CSTP have indicated high rates of lack of compliance, but much better data in protocols that involve a 1-hour waiting period in the lab. After this waiting period, the participant will continue on with physiological equipment attachment and catheter insertion. Physiological equipment (Criticare 506DNP3R, includes blood pressure cuff and SpOv2 sensor) will continuously measure BP/HR by trained Research Assistants or the study PI.

Self-report measures for tobacco product evaluation: Self-report measures were based on established batteries used by VCU CSTP and others (e.g., (Spindle et al., 2018). Four of the five measures use a computerized visual analog scale (VAS) containing a word/phrase in the middle of a horizontal line with "not at all" on the far left and "extremely" on the far right. Participants will record responses by clicking on any point on the line, with scores expressed as a percentage of total line length (i.e., 0-100). Nicotine abstinence symptoms will be assessed via the Hughes-Hatsukami withdrawal scale (Hughes and Hatsukami, 1986). Craving will be assessed by the Tiffany Drobes-QSU Brief consisting of 10 items involving 2 factors: (1) intention to smoke a cigarette and (2) anticipation of relief from abstinence symptoms by smoking (Tiffany and Drobes, 1991). Additional VAS questionnaires will include the Direct Effects of Nicotine (Cappelleri et al., 2007; Evans et al., 2006) and the Direct Effects of ECIG-use scales (10 items; adapted from (Foulds et al., 1992; Pickworth et al., 1994). The fifth questionnaire (the general labeled magnitude scale, gLMS; adapted from (Green et al., 1993) will assess the flavor sensation, harshness/irritancy, and throat hit provided by the tobacco product using a category-ratio scale with 7 semantic labels ranging from (0) "no sensation" to (100) "strongest imaginable sensation of any kind." The questionnaire will be administered via pen and paper after the two tobacco product use bouts in each session.

An additional questionnaire will assess changes in expectancies after product use. The questionnaire uses items from the Smoking and Vaping Consequences Questionnaires – Brief (Hendricks et al., 2015) as well as the Comparing E-Cigarettes and Cigarettes questionnaire (Hersberger et al., 2017). Responses range from "completely unlikely" to "completely likely". Depending on which product was assigned for the session, either the vaping (VCQ-B) or smoking (SCQ-B) items will be used.

Product consumption: The participant will use one of the following three products:

- Own brand cigarette
- ENDS: Subox Mini C with 18 mg nicotine salt (protonated)
- ENDS: Subox Mini C with 18 mg nicotine regular (unprotonated)

The product that is used will be based on pre-established Latin-square order procedure (similar to random assignment) to avoid any order effects. For example, a participant may use the Subox Mini C with 18 mg regular (unprotonated) nicotine the first session, own brand cigarette the second session, and Subox Mini C with protonated nicotine on the last session. Participants will use a different product each session and use all 3 products by the completion of the study.

The cigarette will be purchased at a local retailer based on the participant's self-report in the baseline questionnaire of cigarette brand typically smoked. Smokers are often very loyal to a brand, so this will allow for a control condition of understanding standard reactions to cigarette smoking. The ENDS device will be a Subox Mini C, as recommended by VCU collaborators, who have had prior and current success using this device. The Subox will include a solution with either 18 milligrams/milliliter (mg/mL) of nicotine salt (protonated nicotine) or 18 mg/mL of regular (unprotonated) nicotine. The flavor will match their usual brand of cigarettes (tobacco-flavored or menthol-flavored).

Using a stopwatch, research assistants will instruct participants to take one puff of the tobacco product (cigarette or ENDS) every 30 seconds for 5 minutes. Participants will also complete another set of questions involving evaluation of the product consumed and nicotine withdrawal symptoms. Next, participants will be given 90 minutes to use *ad lib*, i.e., as much as desired. Smoking/vaping sessions will be videorecorded to allow for measurement of puff topography (puff duration, inter-puff interval, etc.). Final questionnaires will be completed. The participant will then be reminded of their schedule for the next session, if another session remains.

Experimental session timeline (approximate times):

- Participant arrives, CO test to confirm tobacco abstinence
- 1-hour waiting period (to help ensure nicotine abstinence), then the rest of the session will begin, as described below
- 0 Hr 0 min - Attach physio equipment, insert catheter, begin questionnaire administration
- 0 Hr 30 min - record Carbon Monoxide
- 0 Hr 35 min - 10 puffs from product (30s inter-puff interval)
- 0 Hr 45 min Record Carbon Monoxide, 2nd set of questionnaire administration
- 1 Hr 05 min record Carbon Monoxide, 3rd set of questionnaire administration, ad lib use period begins (undirected use, participant can use as little or as much as they like)
- 2 Hr 35 min (ad lib period ends)
- 2 Hr 40 min Record Carbon Monoxide, 4th set of questionnaires
- 2 Hr 45 min Remove Catheter, Stop Physio Monitoring
- Payment
- Reminder of next appointment or thank participant for completion of study

Compensation: Participants will complete a W9 at their initial screening visit. Participants will receive $75 after completing the first session, $100 after completing the second session, and

$125 after completing the third session (not counting the first lab visit for screening), resulting in a total payment of $300. If a participant chooses to leave the study early, he or she will keep the amount earned up to that point. In addition, if a session must be discontinued for reasons beyond the control of the participant (e.g., difficulties with catheter insertion), the participant will be paid for the time spent complying with study conditions before the session began ($15) and also the time spent in the laboratory ($15/hour). The compensation amount of $300 was chosen because of the number of hours that participants are asked to be in the laboratory (12.5 hours), which does not include the 12 hours that we ask them to abstain from tobacco products prior to each lab session (which can be very unpleasant for regular cigarette smokers). Thus, the compensation is felt to be appropriate.

Risks to subjects: The protocol uses established methods and procedures and involves only minimal risks to participants. Twelve hours of tobacco abstinence may cause mild discomfort and nicotine abstinence symptoms, but is not medically dangerous. Symptoms may include: irritability, anxiety and restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. The risks of using ENDS/tobacco products/nicotine are routine for the target population. As participation involves consumption of widely available, legal, over-the-counter products that can reduce the harm associated with their current nicotine use, they do not involve significant risks to participants. Risks of nicotine use by nicotine-naïve individuals include sweating, lightheadedness, dizziness, nausea, vomiting, and nervousness. These effects are unlikely in individuals who use nicotine-containing products regularly. In addition, some people who use e-cigarettes have reported experiencing seizures. Some of these individuals reported a prior history of seizures or using other substances at the same time as their e-cigarette. In many cases e-cigarette use has led to respiratory illnesses such as difficulties breathing, shortness of breath and/or chest pain before hospitalization. In some cases, e-cigarette use has led to death, and the Centers for Disease Control and Prevention has advised people to stop vaping. In some cases symptoms of mild to moderate gastrointestinal illness such as vomiting, diarrhea, or fevers or fatigue have been reported.

It is unlikely that the questionnaires will pose any potential risk or discomfort (no sensitive questions are asked). Sessions are relatively short and can be completed at the participants' own pace. With any research, there is always risk of loss of confidentiality. However, the risk is very low for the reasons listed below.

Steps taken to minimize risks / harms: Participant safety and rights will be protected by highly trained staff. Participants will be informed of the potential symptoms of nicotine abstinence/withdrawal and will be told they are free to leave the study at any time.

An additional set of respiratory health questions will be administered by the nurse and/or RA to the participant at screening and then again prior to beginning each session. This will essentially minimize risk as these questions will serve as a supplementary screening tool which will help to determine whether the participant is in good health or ineligible for the study. These questions are included as an attachment (Additional Respiratory Questions). If 1 or more symptoms have increased since the participant's last visit, symptoms will be flagged for review by the medical monitor and will need to be reviewed prior to the participant's next session. If 3 or more symptoms have increased since the last visit, the medical monitor will need to be called in before the session can proceed.

In addition, non-invasive computerized monitoring equipment allows for minute-by-minute, real time monitoring of participants' heart rate (HR) and blood pressure (BP). Research personnel will be instructed to alert biorepository staff if HR exceeds 120 beats per minute, if systolic BP exceeds 150 mm Hg, or if diastolic BP exceeds 100 mm Hg. If HR and BP become elevated, research personnel will be instructed to alert the PI and the session will be stopped. The medical monitor will be available for consult during study sessions if needed. If systolic BP exceeds 180 or diastolic BP exceeds 120, 911 will be alerted. Emergency medical coverage is available across the street. Emergency medical care is available of the expense of the subject and/or their insurance. If systolic BP is between 150-179, diastolic is between 100-119, or HR is over 120, the subject will be monitored until these vital signs are reduced. If this does not occur within 1 hour, 911 will be called. These are anticipated to be very unlikely occurrences, as we exclude participants with resting HR above 110 BPM, systolic above 140, and diastolic above 100, and they are regular smokers in withdrawal consuming levels of nicotine that should be within or below their standard range.

In regards to nicotine abstinence symptoms, the products administered will likely alleviate these risks. Participants will be provided with water at all times.

Participants will be able to view all questionnaires used in sessions before attending sessions, and will be informed of the length of each session. If participants do not want to answer the questionnaires, or feel the length of the sessions are too long, they can choose to not participate.

Data Storage: Risk of loss confidentiality will be minimized by only connecting participant data to participants by alpha numeric identifiers. These data can only be linked with identifiable information by using a key that is stored in locked cabinets. REDCap is a secure web application that is approved for compliance with 21 CFR Part 11, FISMA, and HIPAA. (See https://www.project-redcap.org) Documents completed on paper will be secured in a file cabinet in a locked lab room. Research staff will not release any participant study information to others without signed written approval from a participant. Video recordings will only be stored locally and will be deleted 5 years after completion of the study.

Data are identified by alphanumeric code only. Participants' names are not directly linked to data. An alphanumeric code is assigned to each participant when they provide informed consent, and the numeric part of the code relates to the order in which the individual consented. The alphanumeric code is used in place of identifying information on all subsequent documents/data forms. A key is maintained so that we can demonstrate that a particular data set is associated with a particular consent document. The key and consent documents are kept separately from one another and separate from all data. Access to the key and the consent documents is restricted to study investigators and staff who conduct the study with the participants, so are already familiar with the participants and observe the participants as data are collected. Data keys will be destroyed 5 years after completion of the study.

Data Analysis: Analysis will begin with cleaning, outlier assessment, and normality assessment. Descriptive statistics will be examined for all variables. Similar to prior research (e.g., (Harrell et al., 2016; Spindle et al., 2018), Repeated Measures Analyses of Variance (ANOVAs) will be

used for each dependent variable. There are three within-subject tobacco products (own-brand cigarette, ENDS with unprotonated nicotine, ENDS with protonated nicotine) and four within-subject time points (pre-use, post-directed 10 puff session, pre-*ad lib* use session, post-*ad lib*). Three (condition) x four (time) repeated measures ANOVAs will assess plasma nicotine and heart rate (HR). Questionnaire items (or craving factors) will be examined individually using separate ANOVAs. Analyses conducted on the Hughes-Hatsukami Withdrawal scale, the Tiffany Drobes Questionnaire of Smoking Urges, and the Direct Effects of Nicotine (DEN) have 4 levels of time. The Direct Effects of E-cigarettes scale, unlike the DEN, only assesses reactions to the tobacco product and thus will have only 2 levels of time. Videorecordings will be evaluated via established methodology (Blank et al., 2009).

Any violations of sphericity will be adjusted using Huynh-Feldt corrections. In order to maintain statistical power and limit type 1 error for plasma nicotine, HR, and subjective effects, planned contrasts (paired samples *t*-tests) will be conducted across conditions at the two time points immediately after each use bout (e.g., each post-use session). At these two post-use timepoints, the mean value for each outcome measure in the protonated nicotine condition will be compared to the corresponding mean values in the unprotonated nicotine and cigarette conditions. Because these comparisons are non-orthogonal, a Bonferroni correction will be applied (Keppel, 1991).

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