

## **RVA-Flavors Protocol**

**Title:** Predicting Effects of ENDS Flavor Regulations on Tobacco Behavior, Toxicity, and Abuse Liability among African American Menthol Smokers

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1. **Background:** Black/African Americans (AA) have the highest tobacco-related cancer incidence and mortality rates of any racial/ethnic group. Over 70% of AA smokers smoke menthol as their usual brand, compared to 20% for White smokers. Menthol is the only characterizing flavor allowed in cigarettes under current federal regulations, and menthol use is associated with progression to established cigarette smoking as well as more difficulty quitting. Evidence regarding the effects of electronic nicotine delivery systems (ENDS, i.e., e-cigarettes) suggests these products may be a less harmful alternative to cigarettes. Little work has examined how ENDS uptake affects tobacco use and associated toxicity among AA smokers, particularly those who smoke menthol. Recently, FDA began regulating closed-system devices like JUUL, which have captured over 70% of the ENDS market and contributed to dramatic increases in youth ENDS use. As of early 2020, flavored ENDS cartridges (small, enclosed unit used as part of an ENDS) other than menthol/tobacco are banned in the US. However, to achieve its public health mission, the FDA must balance restricting access to ENDS flavors that appeal to youth with the need for evidence on “whether and how certain flavors may help adult cigarette smokers reduce cigarette use and switch to potentially less harmful products” (FDA, 2018). Understanding the potential of ENDS to reduce the public health burden of combusted tobacco use equitably requires a targeted study to predict how future ENDS flavor regulations will impact AA menthol smokers.

The current study will evaluate whether ENDS menthol flavor availability affects measures of tobacco use, biomarkers of cigarette/ENDS exposure, and addiction among AA menthol smokers (N=210) by performing a 3-arm, parallel-group, 6-week clinical trial of ENDS provision with follow-up to 30 days. JUUL devices with compatible cartridges at 5% nicotine, which our team has extensively evaluated, will be provided. Study arms will differ by potential FDA regulations on ENDS flavor availability: 1) the current market where only menthol and tobacco flavored ENDS cartridges are available; 2) a market where only tobacco flavor is available, and 3) a market with only unflavored cartridges. Study visits will occur weekly beginning 1 week prior to randomization with daily tobacco use monitoring throughout and biomarker/self-report data collection at each weekly visit. AA menthol smokers are disproportionately harmed by tobacco products and could experience significant health benefits from increased availability of well-regulated ENDS.

Results of this work will help FDA make predictions about the impact on AA menthol smokers of moving from the current regulatory market for cartridge-based ENDS where menthol and tobacco are available, to one where only tobacco or no flavors are available. Answers to these questions will address FDA's priorities in behavior, toxicity, and addiction, and will provide new data regarding the consequences of potential FDA regulatory actions on menthol flavor ENDS to help maximize health-promoting effects and minimize unintended consequences among AA menthol smokers.

## 2. Objectives:

The specific aims of our study are to:

- 1) Compare the effect of ENDS flavor availability on patterns of tobacco use behavior. H1: Cigarettes per day will be lowest and ENDS use (puffs per day) will be highest in the M+T\_Reg condition relative to other conditions.
  - a. Primary outcome: Change in average daily cigarette use from Week 0 (prior to randomization) vs. Week 6 (defined as number of cigarettes smoked in the past day, collected via daily text survey, averaged over the previous 7 days)
  - b. Secondary outcome: Change in average daily ENDS use from Week 1 (following randomization) vs. Week 6 (defined as number of ENDS puffs in the past day [daily times used \* average puffs per time used], collected via daily text survey, averaged over the previous 7 days)

- 2) Quantify the effect of ENDS flavor availability on biomarkers of cigarette/ENDS exposure (expired air carbon monoxide [CO], urine cotinine/NNAL, and urine propylene glycol [PG]). H2: Biomarkers of exposure to cigarettes (NNAL/CO) will decrease and from ENDS (PG) will increase most in the M+T\_Reg condition.
    - a. Primary outcome: Change in CO exposure from Week 0 (prior to randomization) vs. Week 6
    - b. Secondary outcomes: Change in NNAL exposure from Week 0 (prior to randomization) vs. Week 6; Change in PG exposure from Week 0 (prior to randomization) vs. Week 6.
  - 3) Test the effect of ENDS flavor availability on addiction/abuse liability using validated behavioral economic instruments at multiple time points during the trial. H3: Smokers will be (a) willing to pay more money for ENDS in the M+T\_Reg condition and (b) willing to substitute from cigarettes to ENDS earlier in the M+T\_Reg condition.
    - a. Primary outcome: Willingness to substitute from cigarettes to ENDS (at Week 6)
    - b. Secondary outcome: Willingness to pay for ENDS (at Week 6).
3. **Overview of Design.** This is a 3-arm, parallel group, 6-week clinical lab study of ENDS provision with a 30-day follow-up post-intervention among AA menthol smokers. We aim to have equal allocation by study arm. Study arms will differ by potential FDA regulations (Reg) on ENDS flavor availability as follows, with nicotine concentration and ENDS device held constant: 1) the current market for cartridge-based ENDS where only menthol and tobacco flavors are available for consumers to choose from (M+T\_Reg); 2) a market where only tobacco flavor is available (T\_Reg), and 3) an unflavored control condition (U\_Reg), representing a market where all characterizing ENDS flavors are banned.
4. **Participants.** A total of 210 AA community volunteers who currently use menthol cigarettes will be randomized in this study. We will attempt to recruit an equal number of men and women and equal numbers above and below 100% of the Federal Poverty Level to explore differences in condition effects across gender and income. To achieve this number of participants, the VCU Wright Center informatics team will provide contact information sourced from the EMR for ~5000 patients who fit the study criteria. These patients will be invited to participate in the study.
- a. Inclusion criteria:
    - i. ≥21 years of age (id-verified)
    - ii. identify as AA (single or multi-race)
    - iii. have used ≥5 CPD for ≥1 year
    - iv. biochemically confirmed cigarette smoking status
      1. expired air CO >5 ppm
      2. positive urine cotinine result at screening (defined at least 200 ng/ml; NicAlert cassette test)
    - v. regular cigarette brand is flavored to taste like menthol or mint
    - vi. ENDS use in the past 3 months
    - vii. report no intent to quit smoking in the next 6 months (**unwilling to quit**)
    - viii. previous quit attempt using an evidence-based quit method (**unable to quit**)
    - ix. have a working mobile phone with a texting/data plan
    - x. are willing receive phone calls/text messages and complete internet-based/online surveys related to the study.
    - xi. read and write in English
  - b. Exclusion criteria:

- i. are unwilling to use JUUL/pod-based ENDS as part of the trial
- ii. unstable or significant medical condition in the past 12 months (e.g., recent heart attack, stroke, severe angina including high blood pressure if systolic >159 or diastolic >99 observed during screening; inpatient psychiatric treatment; uncontrolled seizures)
- iii. report any other illegal drug use in past 30 days, **not** including marijuana
- iv. report intent to become pregnant or current pregnancy/breastfeeding (pregnancy confirmed via urinalysis)
- v. report any other condition that may affect participant safety or not allow them to fully participate in the study (e.g., contraindication to spirometry; allergy to propylene glycol/vegetable glycerin).

5. **Products.** Randomized participants will receive an ENDS supply consistent with their condition throughout the 6-week intervention period.

- a. ENDS. For all conditions, ENDS batteries will be purchased directly from JUUL Labs. Inc. Across ENDS regulatory conditions, ~5% nicotine pods will be used to control for nicotine delivery and due to availability of pharmacokinetic data from similar products (Hajek, Pittaccio et al., 2020; Maloney, Crabtree et al., 2020). As unflavored pods are unavailable for purchase from JUUL and to ensure all conditions have the same ENDS operating characteristics/nicotine delivery, for all conditions we plan to purchase unfilled JUUL compatible pods and verify the similarity of heating element and other product characteristics to JUUL products using resources at the CSTP (Project 1 Investigator: Dr. Talih). We will purchase tobacco, menthol, and unflavored ENDS liquid at 5% nicotine from a reputable supplier. We will verify the equivalence of the liquid characteristics (protonated vs. unprotonated nicotine; PG/VG ratio) relative to currently marketed menthol and tobacco-flavored JUUL pods. We have experience purchasing and independently testing unflavored/flavored liquid (Barnes, Bono et al., 2017; Cobb, Lopez et al., 2019).
  - i. If supply-chain/access issues occur, we may substitute our JUUL compatible pods with actual JUUL Labs. Inc. pods in menthol and tobacco flavor. These substitutions can only occur for the M+T\_Reg and T\_Reg conditions. If unflavored pods become unavailable, individuals randomized to U\_Reg will have either their product supply stopped (if already randomized) or be randomized to either the M+T\_Reg and T\_Reg condition.
- b. Product Instructions. At each in-person visit during the intervention period we will instruct participants: “We are providing you with an e-cigarette in [condition-specific flavors] over the next [X] weeks to be used as a substitute or complete replacement for your own brand cigarettes. We want to understand how you use these specific e-cigarettes as well as your own brand cigarettes when they are the only products available to you. Therefore, please refrain from using all other nicotine/tobacco products and other e-cigarette flavors for the duration of the study. If you use anything else, it is important that you tell us what you used.”
- c. Product Distribution. Following randomization, participants will be provided with two pre-charged JUUL batteries with a USB-compatible charger and USB-power outlet adapter. All pods will be provided in sealed single-use containers. A 2018 convenience survey of adult JUUL users indicated that daily users consume on average 10 pods per month (i.e., <1 pod/day; Leavens, Stevens et al., 2019). This data and our experience with distributing ENDS to smokers (P50DA036105-Project 3) led to us estimate individuals may use up to 1 pod/day. At randomization and week 3 visit participants will receive ~3

weeks worth of pods (21 pods) plus 11 additional pods to allow for product loss and/or malfunction (~32 pods total). All participants will receive brief instructions on how to use their ENDS device and taste-test their assigned flavor(s; at least 4 directed puffs per flavor). Individuals randomized to the M+T\_Reg condition will choose how many pods of each flavor they prefer to receive. To minimize sharing, we will emphasize that these products are investigational and provide an incentive for returning used/unused pods (\$30 for returning >70% of the supplied ENDS product at each visit). We may incorporate returned products into each new week's supply for that participant. This strategy has been used successfully by our Co-I Dr. Donny at Wake Forest University (not engaged with study). At the conclusion of the Week 6 visit, all participants will be provided with tobacco prevention/cessation resources, and they will be able to keep their ENDS devices/charging materials and up to 4 unused pods in their condition-specific flavors.

- d. Product Labeling. Distributed products for all conditions will be labeled with the following.

-Participant ID (PID: )

-Date of visit

-Visit Number (Visit: )

For JUUL-compatible pods that are filled by the study staff, each pod once filled with liquid will be stored in a single use sealable bag labeled with an additional label:

-VCU Lot Number (VCU Lot: )

-VCU Liquid Lot Number (LIQ Lot: )

-Pod preparation date (PREP: )

When distributed to participants, up to 4 single pod bags will be placed inside a larger bag with the same two labels included.

- e. Other Product Information: E-cigarette companies have to apply to the Food and Drug Administration (FDA) and be approved for sale in U.S. markets. In June 2022, the FDA denied the marketing application from JUUL, the manufacturer of the e-cigarettes used in this study. The FDA determined that JUUL did not provide enough evidence about the toxicity of its e-cigarette device and pods in its application. However, the FDA has not received clinical information to suggest an immediate hazard associated with the use of JUUL devices or JUUL pods. The FDA decision to ban the sale of JUUL is not final yet due to ongoing legal disputes. When and if the FDA's decision to ban JUUL is final, it will be illegal to sell JUUL products. However, it will still be legal for researchers to study these products and for participants to use them.

- i. The above text has been added to the informed consent form for this study under **Most Common Risks and Discomforts** to address recent developments regarding JUUL products from the FDA.

- ii. An investigational tobacco product application describing the products provided and procedures used in this study was submitted for review to the FDA Center for Tobacco Products on 7/22/2022.

6. **Recruitment and Enrollment**. Participants will be recruited by institutional review board-approved advertisements as in previous studies conducted at the VCU BHRL/CSTP and by word of mouth. The BHRL and CSTP Tobacco User Registries are available to aid recruitment efforts (>6000 records). Interested individuals will either 1) complete a pre-screener specific to this study (see Pre-Screener measures) or 2) access the BHRL/CSTP website and/or complete a screening survey (pre-screen) specific to these registry protocols online or via phone to determine initial eligibility.

We also will recruit from a list of VCU Medical Center patients who meet study eligibility criteria as determined by the Cerner EMR and/or Massey Cancer Center Informatics Team. Tobacco use history is recorded in each patient's social history. Additionally, a text data mining algorithm may be used to search for key terms in provider notes (e.g., tobacco, smoking, quitting smoking, e-cigarette) to identify potential participants. Once we have this list of potential participants we will proactively recruit.

Proactive recruitment strategies will include the following:

- From the EMR-generated list of potential participants, our research personnel will call individuals and/or leave up to 2 voice-mail messages introducing them to the study and the pre-screener.
- From the EMR-generated list of potential participants, our research personnel will mail individuals a letter (see Mail Invitation), introducing them to the study, as well as information about how to complete the pre-screener.
- After the initial pull of potential participants for this study, we will ask to re-run this EMR-generated list about 1x/month to learn if there are any new potential participants.
- No data from the list will be stored in the project. The list will be used to contact potential participants and then destroyed after the contacts above have been completed.

7. **Consent process.** Informed consent for the prescreening will be obtained prior to completing any questions and informed consent for the full study will be obtained at the in-person screening visit prior to completing any research activities. At the in-person visit, the informed consent document will be either be played via a pre-recorded powerpoint tool or read aloud by a trained research staff. Prior to participant signature, research staff will ensure all questions and concerns about the study are answered fully. This process will be documented via administrative forms in REDCap and with signed paper documents which will be kept in a locked file cabinet separate from other research data during and after data collection.
8. **Study Procedures.** Study participation will consist of three primary phases (see table below): 1) screening/baseline, 2) experimental/intervention period, and 3) 30-day follow-up during which participants will not be provided with study product nor will be given explicit recommendations to change their tobacco use behavior.
  - a. Screening and baseline. Once the participant is deemed potentially eligible from the online/phone-based screening survey (pre-screen; via one of the pre-screener measures included in the current protocol or BHRL/CSTP Tobacco User Registry survey), an in-person screening/baseline assessment will be scheduled. Then, an informed consent will be obtained for the full study, and participants will be asked to complete baseline forms and measures (e.g., urinalysis/expired air CO) to assess/confirm eligibility.
    - i. During the informed consent procedure, all participants will be provided information regarding an optional project (funded within Virginia Youth Tobacco Projects Program (VYTP), sponsored by the Virginia Foundation for Healthy Youth; PI: Dr. Shawn Jones, VCU Psychology Department).
    - ii. The VYTP part of the study focuses on the impact of racial socialization, identity, media perceptions, and racial discrimination on tobacco use. More specifically, this project aims to understand how race-related factors during adolescence impact tobacco use in adulthood. Participants are eligible to participate in this part of the study they are aged 21 or older. The only additional participant activities related to the VYTP part of the study are the completion of additional questions (~25 min) at the screening/baseline session. Engagement in this part

of the study is completely optional and will have no bearing on full study participation. Participant payments for the VTYP part of the study will be sourced from a separate fund/index.

- iii. Participants who meet all eligibility criteria at the in-person screening/baseline assessment, will be instructed to smoke their usual brand of cigarettes normally for the next 7 days, avoid using any other tobacco products, and complete daily text surveys to report their CPD. The primary purpose of this baseline period is to familiarize participants with the data collection procedures/system, reduce dropout prior to randomization, and collect a baseline measure of CPD. Participants will also be provided with contraception resources at this point in the study to help prevent pregnancy during the study.
- iv. Participants who are asked to complete the baseline period will be eligible for randomization if they:
  - 1. average CPD > 4 on the 7 prior daily surveys responded to
  - OR**
  - average CPD > 4 on the 7-day timeline follow back questionnaire asked at randomization
  - 2. attend randomization visit in the study window
- v. Participants who are ineligible to participate in the main study (at screening/baseline or prior to randomization) will be informed that based on their responses:
  - 1. the current study is not a good fit for them
  - 2. a screening payment (and if applicable daily survey and/or randomization visit payment) for their time and effort will be provided
  - 3. tobacco prevention/cessation resources will be provided.

b. Experimental/intervention period.

- i. Approximately 1 week after consent/baseline (Week 0), participants will return to the study site to be randomized to 1 of 3 conditions with equal probability using a computer-generated sequence. Condition assignment will be unblinded due to the nature of study conditions, but allocation concealment will be used to limit biased assignment.
- ii. At Week 3 and 6, participants will return used/unused product and at Week 3 make selections for product dispensation for the subsequent weeks (could occur at the study site or in-person at their home).
- iii. Daily text surveys to measure tobacco/study product use will also continue throughout the intervention period.
- iv. Participants will complete self-report/behavioral measures at the end of each study week (sent via email/text for remote visits or completed in-person at the study site). These surveys will also record changes in concomitant medications, and assess any adverse events. If indicated, study staff will follow-up with participants via phone or in-person regarding responses provided.
- v. Physiological measures and expired air CO and spirometry will be measured and urine will be collected for biomarker assessment (NNAL, cotinine, propylene glycol) at the end of Weeks 0, 3, and 6. Heart rate, blood pressure, and spirometry will only be measured if participants attend subsequent visits at the study site.

- vi. To capture ENDS and other study product-related experiences that are not well-assessed by current behavioral and self-report measures, a brief recorded semi-structured interview will be conducted via phone/Zoom at Weeks 2 and 5.
- vii. Of note – For at home visits (Week 3 and 6; per participant preference), study staff will remain outside the participants' home and provide/receive study-related materials (cooler containing urine sample materials; bag containing CO monitor/END-related materials) at the building door/main entrance. For these at home visits, participants will receive an online survey to containing weekly self-report measures.
- viii. At the conclusion of the Week 6 visit, all participants will be provided with tobacco prevention/cessation resources. Participants will be able to keep their ENDS devices/charging materials and up to 4 unused pods in their condition-specific flavors.
- ix. Following randomization and at the conclusion of the study period (two unique times), all participants will be sent a greeting card (see approved scripts).
- c. 30-day Follow-up. Participants will be asked to complete a reduced set of self-report measures via an online survey.

9. **Measures.** Participants will complete the measures listed on the measures timeline below.

	<u>Screening /Baseline</u>	<u>Rand</u>	<u>Weekly study visits</u>						<u>30-d FU</u>
<b>Study Week</b>	<b>-1</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>~10</b>
<i>Study Visit Window</i>	NA	-1/+7	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3	-7/+7
<i>Approximate visit length (min)</i>	60-120	60-120	<60	<60	60-120	<60	<60	60-120	<60
<i>Mode: InPS=in-person at study site, IPH=in-person at home, Rem=phone/online</i>	InPS	InPS	Rem	Rem	InPS or InPH+Rem	Rem	Rem	InPS or InPH+Rem	Rem
<b>Tobacco use behavior (Aim 1)</b>									
Daily Tobacco Use (daily text surveys)		x	x	x	x	x	x	x	
7-day Tobacco Use TLFB		x	x	x	x	x	x	x	x
ENDS liquid consumed (weight via products returned)					x			x	
<b>Cigarette/ENDS (Aim 2)</b>									
Expired air CO	x*	x			x			x	
Urinary cotinine, NNAL, PG	x*	x			x			x	
<b>Abuse liability/addiction (Aim 3)</b>									
Cigarette/ENDS purchase tasks (n=3)		x (cigarette-only)			x			x	
<b>Other self-report measures</b>									
Demographics, tobacco use history, medical history	x								
Drug/alcohol use	x								
Tobacco perceptions/attitudes	x								
Stage of change/quit confidence		x			x			x	x
Environmental smoke exposure	x				x			x	
Cigarette/ENDS dependence		x (cigarette-only)			x			x	x
Withdrawal/stress		x	x	x	x	x	x	x	x
Respiratory measure		x			x			x	x

ENDS evaluation		x	x	x	x	x	x	x	
Adverse events		x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x
End of intervention								x	
Follow-up form									x
<b>Semi-structured interview</b>				x			x		
<b>Other physiological measures</b>									
Spirometry		x			x <sup>#</sup>			x <sup>#</sup>	
Height	x								
Heart rate, blood pressure, weight	x	x			x <sup>#</sup>			x <sup>#</sup>	
Pregnancy test	x								
<b>VYTP Measures:</b> Racial socialization, identity, media perception, discrimination and tobacco use	x <sup>^</sup>								

\*Semi-quantitative cotinine and CO are collected at in-person screening to confirm eligibility by confirming exposure to nicotine and cigarettes

<sup>^</sup>Only individuals who opt-in to the VYTP project and are eligible to participate in this optional ancillary study (based on self-reported age) will be asked to provide self-reported data about the impact of racial socialization, identity, media perception, and racial discrimination on tobacco use during the screening/baseline session.

<sup>#</sup>Spirometry, heart rate, blood pressure, and weight will only be collected at in-person visits but not if participant chooses the remote option to complete this visit)

- a. **Screening and baseline assessment:** We will assess DEMOGRAPHICS, TOBACCO USE HISTORY/QUIT ATTEMPTS, MEDICAL HISTORY including health/psychiatric conditions (e.g., Medical History Form used in P50DA036105-Project 3), DRUG/ALCOHOL USE (e.g., NIDA Quick Screen; NIDA, 2012), TOBACCO PERCEPTIONS/ATTITUDES (see Bono et al., 2019), and ENVIRONMENTAL SMOKE EXPOSURE (e.g., Nondahl et al., 2005) using standardized items from PhenX, national surveys (e.g., PATH; BRFSS; TUS-CPS) and items/measures adapted specifically for ENDS (Dawkins et al., 2013). Several of these measures are repeated during the intervention and follow-up period to assess change over time.
- b. **Experimental/intervention period:**
  - i. Participants complete TEXT SURVEYS once per day for the week prior to and throughout the 6 weeks where study product is provided. Please note, these texts include limited items in order to increase compliance and decrease burden as in (Donny et al., 2015). The survey assesses previous day cigarette smoking, ENDS use, and other tobacco/nicotine use. This information can be used to better characterize study product use patterns as JUUL batteries do not have an integrated automatic puff counter (unlike the device used in P50DA036105-Project 3).
  - ii. At weekly visits (0-6), a more intensive 7-DAY TIMELINE FOLLOW-BACK PROCEDURE (TLFB; Sobell & Sobell, 1992) will be performed to measure these same outcomes as well as use of other tobacco products, alcohol, and cannabis.
  - iii. We will also weigh ENDS products returned at Weeks 3 and 6 to determine the volume of ENDS LIQUID CONSUMED (as in Cobb et al., 2020; Ohaus Model PA163C; 0.000 g detection limit).
  - iv. Immediately following randomization, participants will be asked to complete ~4 directed puffs of each of assigned ENDS available for their condition (order randomized for those with two flavors). Prior to testing, a brief video will be played by staff members describing how to use the device and associated

materials. BRIEF SUBJECTIVE MEASURES OF ACCEPTABILITY/FLAVOR LIKING (I.E., ENDS EVALUATION) will be administered after each flavor is tested (Kim et al., 2016).

- v. OTHER ENDS EVALUATION MEASURES will also be administered weekly to understand positive and negative effects of study product use (including sensory effects) (e.g., adapted from Hatsukami et al., 2013), and other side effects (developed as part of P50DA036105-Project 3).
  1. These questionnaires will be supplemented by SEMI-STRUCTURED INTERVIEWS performed via phone at Weeks 2 and 5 weeks post-randomization that are aimed at assessing potential perceived barriers/perceived benefits of study product use not captured in available assessments. We plan to interview all randomized participants at these two timepoints. If the participant consents to participate in this ~15 min discussion, it will be audio-recorded (using Zoom). Audio-recordings will be maintained in locked file cabinets and/or secure electronic location until they are transcribed and then the audio-recordings will be destroyed. All names/direct identifiers will be removed from the audio-recording transcriptions.
- vi. OTHER SELF-REPORT MEASURES administered at randomization and weekly visits include STAGE OF CHANGE (e.g., Prochaska & Goldstein, 1991), cigarette/ENDS dependence (e.g., Penn State Cigarette Dependence Measure; Foulds et al., 2015), withdrawal/stress measures (e.g., Perceived Stress Scale; Cohen et al., 1983; Minnesota Nicotine Withdrawal Questionnaire; adapted from Hughes & Hatsukami, 1986). A respiratory measure will be assessed during Weeks 0, 3, 6, and during the online follow-up survey (Clinical COPD Questionnaire; van der Molen et al., 2003).
- vii. CHANGES IN ABUSE LIABILITY related to study product assignment, three purchase tasks (Jacobs & Bickel, 1999; MacKillop et al., 2008) will be completed at Weeks 0, 3, and 6: own brand cigarette, condition-specific ENDS, and cross-product purchase tasks. In each version, participants will be asked how many times they would consume a puff of a tobacco product (e.g., cigarette and/or ENDS) at each of 25 different prices offered (range \$0.00-\$20.48). In addition to measuring abuse liability for cigarettes and condition-specific ENDS, cross-product abuse liability will also be measured using a cigarette purchase task modified to assess how much participants are willing to substitute consumption of ENDS for their own brand cigarette.
- viii. ADVERSE EVENT/CONCOMITANT MEDICATION monitoring will be assessed after screening/enrollment at each weekly visit using comprehensive forms and procedures developed as part of P50DA036105-Project 3 to note the nature, relatedness, outcome, and action taken for all adverse events noted as part of this study (see DSMP for detail). For remote visits, participants will receive an additional study-related phone call to follow-up regarding any adverse events or changes in medications reported.
- ix. An END OF INTERVENTION questionnaire at week 6 will quantitatively assess participant reactions to their study product, reasons for non-compliance during the study, and potential reactions to future FDA regulatory policy.
- x. A FOLLOW-UP SURVEY FORM is included with the follow-up survey to allow participants to elaborate on their experiences since ending the intervention period.

- xi. BIOMARKERS (n=4) of tobacco/ENDS-related toxicant exposure will be assessed: (1) expired air CO, (2) urinary cotinine, (3) urinary total NNAL, and (4) propylene glycol. Expired air CO will be measured using a Micro+™ basic Smokerlyzer® (coVita, Santa Barbara, CA). Expired air CO and urine samples will be assessed at Weeks 0, 3 and 6. Urine samples will be stored for later analysis of quantitative levels of cotinine, total NNAL concentration (sum of NNAL and its glucuronides) as well as creatinine (for adjustment of the biomarker results), and propylene glycol by VCU's Department of Pharmacy using liquid chromatography tandem mass spectrometry techniques (Naidongu et al., 2001; Shah et al., 2009; Shah et al., 2011).
  - 1. For participants who choose to complete in-person assessments at their home (Weeks 3 and 6), researchers will meet participants at their front door/building entrance. Staff will confirm participant identity verbally, and then provide a small cooler/bag containing the CO monitor/device, urine sampling materials, and if needed ENDS product supply. Participants will be asked to return to their home to provide a CO sample (result saved locally on the device), a urine sample, and to return any used/unused ENDS supplies (with the exception of the batteries/charging materials). Participants will return materials to the staff who will then dispense payment for study activities to date.
- xii. OTHER PHYSIOLOGICAL MEASURES (n=4) will also be assessed at screening/baseline and at in-person visits (Weeks 0, 3, and 6) to determine any condition-related effects over time: heart rate, blood pressure (systolic and diastolic), spirometry (e.g., FEV1, FVC) and weight. Height will be assessed once at screening/baseline. PFTs will only be performed for individuals who have not had eye/chest/stomach surgery in the past 6 weeks (assessed at screening/baseline)
  - 1. For participants who choose to complete in-person assessments at their home (Weeks 3 and 6), we will not collect these measures.
- c. 30-day follow-up. Outcomes measured at the 30-day follow-up online survey will repeat several of those measured during the screening/baseline and intervention phases including stage of change/quit attempt history, environmental smoke exposure, tobacco/drug/study product use via 7-day TLFB, adverse events, and cigarette/ENDS dependence.

10. **Compensation.** Completion of daily text surveys is \$1 a day with a \$10 bonus for completing 7 calls in a row for a total possible compensation of \$119 (over 7 weeks). Please note, due to study visit windows at randomization (-1/+7 days) and the week 6 visit (-3/+3 days) it is possible participants may complete up to 10 additional daily surveys during the study period (up to \$20 additional compensation), but this is unlikely and thus not emphasized in the compensation description. Participants will be compensated for compliance in bringing back their used/unused study product (\$30 per visit – Week 3 and Week 6 - for a total of \$60 over the course of the study). The in-person screening and baseline visit is estimated to take 60-120 min (\$40), randomization visit=60-120 min (\$60), week 3 and week 6 visit=60-120 min (\$40 each). Remote visits during weeks 1, 2, 4, and 5 are expected to take <60 min (\$20 each) and the online 30-day follow-up survey is expected to take <60 min (\$20). During week 2 and 5 participants will be paid an additional \$20 per visit for completing the interview. In addition, participants receive a \$75 bonus for completing all study visits as well as parking/traveling compensation (\$10) at

each in-person study visit (total \$40). If participants attend all visits, comply with protocol, and complete the follow-up survey they could earn a total of \$654 (text surveys=\$119, product compliance=\$60, study visits and follow-up survey=\$360, attendance bonus=\$75, parking/travel=\$30). Participants who enroll but later become ineligible or withdraw for any reason can schedule a time to pick up their compensation earned to date at our study site or have us email an Amazon giftcard to them.

If participants opt-in and are eligible to participate in the VYTP project, those who complete these measures will be compensated an additional \$40 at the screening/baseline visit.

If participants are eligible following the in-person screening they will be given 5 referral cards that have our lab information and a number/letter combination on them. The numbers/letters on the cards are linked (by us) to the participant's name/e-mail address. They can give these cards to friends or family members who might want to participate in this study. If someone attends an in-person screening visit with the card, the participant can receive an additional \$20 per returned card, paid in cash or Amazon gift card (email). They will not be told who brought us the card. The referral cards expire after one year.

11. **Sharing Results with Participants.** This study is not intended to diagnose any disease or condition. At any point in the study if results reach a critical value (defined by the medical monitor), such as repeated high blood pressure or low lung function, the research staff and/or medical monitor will discuss the result with the participant, provide them with a letter explaining their results, and advise the participant to seek care from their primary care physician. If the critical value is observed following screening/baseline and adverse event will be created automatically for documentation and medical monitor review. In the event that a person tests positive for pregnancy, the research staff will discuss the result with the participant and urge them to seek prenatal medical care. The research assistant will provide the participant with information about where to receive prenatal care (either with their regular physician or at free clinics).
12. **Statistical Analysis Methods and Sample Size/Power.** Following data cleaning and verification of baseline characteristics equivalence across conditions, analysis of the primary outcomes (Aims 1-3) will follow. Linear mixed (random effects) models will be used to analyze the adjusted association between conditions, time (visit), and each outcome. These models have several benefits over traditional repeated measures ANOVA including more flexibility in handling correlation patterns among the error terms and the ability to examine and estimate within-subject (individual) effects (Krueger & Tian, 2004; Scott, Siminoff et al., 2013). We will use an intent-to-treat (ITT) approach for all analyses and test the sensitivity of our results to missing data using multiple imputation (Allison, 2002). Please note that analysis of our secondary/exploratory outcomes (e.g., liquid weight, spirometry, other self-report items) will largely follow similar methods.

**Aim 1.** This aim tests the hypothesis that participants will report larger reductions in CPD (via daily text surveys) between baseline and week 6 in the M+T\_Reg condition relative to the T\_Reg condition. Using within-subjects and between-subjects analyses with 210 participants (70/condition), we will have 80% power given  $\alpha < 0.05$  to detect differences in CPD between the M+T\_Reg vs. T\_Reg conditions of 50% or larger (e.g., 9 fewer CPD in M+T\_Reg vs. 6 fewer CPD in T\_Reg) assuming a moderate correlation within individuals across visits ( $r \geq 0.50$ ; G Power Version 3.1.4). At week 6, we also predict participants will report taking more puffs per

day from their ENDS in the M+T\_Reg vs. T\_Reg condition. These estimates are based upon P50DA036105-Project 3.

Aim 2. This aim tests the hypothesis that participants will report larger reductions in biomarkers of cigarette exposure (CO, total NNAL), and larger increases in biomarkers of ENDS exposure (PG), between baseline and week 6 in the M+T\_Reg than in the T\_Reg condition. With 210 participants (70/condition), we will be powered ( $\geq 80\%$ ) to detect differences in CO reductions of 50% or larger (e.g., 6 fewer ppm CO in M+T\_Reg vs. 4 fewer ppm CO in T\_Reg). These estimates are based upon P50DA036105-Project 3 and R21CA184634. We also predict that increases in PG will be correlated with reductions in biomarkers of cigarette exposure.

Aim 3. This aim tests the hypothesis that behavioral economic abuse liability indices (Willingness to substitute from cigarettes to ENDS; Willingness to pay for ENDS) will be higher in the M+T\_Reg than in the T\_Reg condition. With 210 participants (70/condition), we will be powered ( $\geq 80\%$ ) to detect differences of 50% or larger at week 6 in the breakpoint, or maximum participants are willing to pay for ENDS (\$1.30 in M+T\_Reg vs \$0.86 in T\_Reg). This study will also be powered to detect similarly sized differences in own-price elasticity, or how much demand for ENDS changes as ENDS prices increase (0.05 in M+T\_Reg vs. 0.08 in T\_Reg), and in cross-product price elasticity, or the willingness to substitute from cigarettes to ENDS as cigarette prices increase (0.07 in M+T\_Reg vs. 0.04 in T\_Reg). These estimates originated from Barnes et al. (2017).

a. VTYP Project Analysis Plan:

- i. Prior to conducting analyses, the descriptive statistics and distributions of each variable will be examined. Every effort will be made to minimize participant attrition and missing data. However, in the event of missing data, analyses will be conducted to examine whether participants with missing data differ from participants without missing data in meaningful ways. Missing data may be addressed using multiple imputation or through use of Full Information Maximum Likelihood (FIML) parameter estimation techniques.
- ii. Aim 1 first evaluates whether racial discrimination and stress positively predict current tobacco use and total tobacco use. In order to evaluate this initial hypothesis, a longitudinal hierarchical linear model (HLM) will be specified in Mplus (or comparable data analysis software) to examine whether racial discrimination and stress predict cigarette and total tobacco use patterns at baseline. Date of tobacco use initiation and demographic characteristics (e.g., sex and income) found to be significantly correlated with our tobacco outcomes will be included in the analysis model as control covariates. This analysis will thus allow for a robust test of whether discrimination and stress experienced during the adolescent period predicts tobacco use at baseline.
- iii. Aim 2 evaluates whether protective factors, racial socialization, identity, and media perception, moderates the effects of predictor variables (discrimination and stress) on current and total tobacco use. Testing Aim 2 will involve an HLM analysis model and testing procedure similar to the analysis model used to test Aim 1 along with the interaction term. Again, any age of tobacco initiation and demographic variables found to be notably correlated with tobacco use will also be included in the analysis model as control covariates. It is expected that these moderation effects will be such that the magnitude of the association between discrimination and stress with tobacco use will be significantly greater (worse) for those who reported lower levels of racial socialization and identity (e.g., low centrality, low private regard) during adolescence.
- iv. Power analysis estimates were based on 5,000 hypothetical datasets simulated

using the Monte Carlo procedures of Mplus Version 7.20. Results showed statistical power will be  $\geq .80$  to detect a significant discrimination  $\times$  socialization  $\times$  tobacco use interaction effect over time if the following expected and reasonable effects are present if the effect of discrimination on tobacco use is at least  $\beta = .2-.3$ , and the resulting discrimination  $\times$  socialization interaction effect on tobacco use over time is  $\beta \sim .24-.25$ . Separate models will be run for discrimination and racial stress and with each protective factor. For continuous measures, a significant interaction will imply moderation, with the size of the estimated coefficient reflecting the moderated change in the effect. Significant interaction effects can be followed up by testing the significance of the intervention effect across various levels of the moderator (e.g., 16th, 50th, and 84th percentile). We plan to examine the influence of age as a potential moderator in the proposed analyses. We do not expect power to detect effects will be impacted substantially by its inclusion.

### 13. Withdrawing Participants

Participation in this study may be stopped at any time by the investigator without participant consent. The reasons might include:

- the investigator thinks it necessary for the participant's health or safety
- the participant is found to not be eligible for the study
- the sponsor has stopped the study
- the participant has not followed study instructions
- administrative reasons require the participant's withdrawal

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