Cover page for Protocol

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Grant Title: Impact of Nicotine Reduction on Adolescent Cigarette Use, Alternative Tobacco Use, and Harm From Tobacco

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Impact of nicotine reduction on adolescent cigarette use, alternative tobacco use, and harm from tobacco

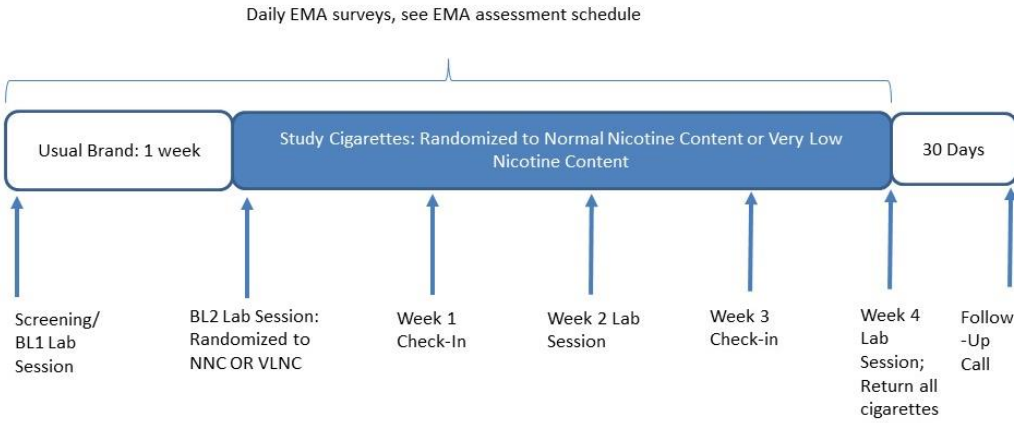
PIs: Cassidy & Colby

1. **Lay Summary**: Adolescents are an important vulnerable population to consider as the FDA moves toward a nicotine reduction policy. Such a policy, which would mandate a reduction of nicotine in all commercially available cigarettes, has the potential to transform public health and greatly reduce the toll of tobacco-related death and disease. Yet, data on the effects of such a policy on cigarette use among adolescents are lacking. Further, the advent of e-cigarettes and the popularity of alternative tobacco products have fundamentally altered the current landscape of nicotine delivery, and these products are widely used by adolescents. Although adolescent cigarette use is at an all-time low in the U.S., this reduction has been mirrored by an increase in e-cigarette use, and multiple tobacco product (MTP) use is the most common pattern of use in youth. Adolescent MTP users are more likely to be dependent on nicotine and to have begun using tobacco earlier than their single-product using peers. Thus, MTP-using youth differ from youth who solely smoke cigarettes in meaningful ways that have implications for responses to a nicotine reduction regulatory policy. In adults, longer-term studies have demonstrated that VLNC cigarette exposure results in fewer cigarettes smoked and reduced toxicant exposure; however, increased use of alternative tobacco products has also been reported. No studies to date have examined the effects of VLNC cigarettes on MTP use or toxicant exposure in youth. This study will use real-time, smartphone-based EMA and laboratory-based assessments to: (1) investigate the effects of cigarette nicotine reduction on cigarette and MTP use, (2) assess the influence of cigarette nicotine reduction on the harms associated with tobacco use, including nicotine and toxicant exposure, respiratory symptoms, perceived health risk and nicotine dependence, and (3) use a combination of laboratory and real-time assessment to investigate the effects of nicotine reduction on changes in withdrawal, craving, and the reinforcing efficacy of cigarettes to characterize the mechanisms by which VLNC use may affect behavior. Overall, this project will help determine the effects of VLNC cigarettes on real-world tobacco use behavior and indices of tobacco-related harm in adolescents, and examining the mechanisms through which nicotine reduction in cigarettes may effect such changes. Such knowledge will contribute to the science base that may inform future policy decisions.

2. **Protocol Narrative**
   a. **Aims & Methodology**
      a) **Aim 1:** To determine the effects of VLNC vs. NNC cigarettes on cigarettes smoked per day and frequency of alternative tobacco product use in adolescent cigarette smokers. We hypothesize that use of VLNC cigarettes will be associated with a decrease in combustible cigarettes smoked per day and an increase in the number of days of alternative combustible and noncombustible tobacco product use.
      b) **Aim 2:** To determine the effects of VLNC cigarettes on nicotine and toxicant exposure, perceived health risk of tobacco products, respiratory symptoms and dependence. We will test the hypothesis that use of VLNC cigarettes will lead to reduced nicotine and toxicant exposure, dependence, and respiratory symptoms in adolescent MTP users.
      c) **Aim 3:** To leverage real-time EMA assessment to determine the effects of VLNC cigarettes on withdrawal and craving, and to determine whether these momentary changes influence alternative tobacco use. We hypothesize that VLNC cigarette exposure may influence momentary changes in withdrawal and craving; and that these will vary both within and across individuals.

3. **Overall Study Design:** A 2-group randomized between-subjects design will be used. Following a phone screening and informed consent procedure, adolescent tobacco users (ages 15-19, N=120) who report smoking cigarettes on at least 28 out of the last 30 days and use of one or more alternative tobacco products in the past 30 days, will complete their first laboratory session (Baseline Session 1 or BL1). After a one-week usual-brand baseline period during which all participants smoke as usual, a second laboratory session will be completed (BL2). At the end of that session, participants will be randomized to switch to either NNC (15.8 mg/g; n = 60) or VLNC (0.4 mg/g) cigarettes (n=60). During the 4-week experimental period, participants will be provided with study cigarettes each week and instructed to smoke only those cigarettes. They will also be told that they may choose to use other nicotine-containing products, such as e-cigarettes and little cigars, during the study. Daily, we will assess all cigarette smoking and use of all other tobacco products (as well as any non-compliant use of non-study cigarettes), and craving, withdrawal, and other factors using a smartphone-based app. Weekly, participants will come to the laboratory to complete assessments of dependence and respiratory symptoms, and behavioral economic assessments. Thirty days after the end of the protocol, participants will be contacted via phone and asked about their use of tobacco products and any changes in their overall health as a safety check. The flow of the protocol is depicted in **Figure 1.** All laboratory measures are shown in **Table 1.**

Figure 1. Protocol Timeline.



a. **Research Cigarettes.** All cigarettes tested will be Spectrum research cigarettes (22nd Century Group, Inc.), which are produced for the National Institute on Drug Abuse (NIDA; NOT-DA-14-004). The two cigarette types tested in the current study will contain 15.8 mg nicotine/g tobacco (normal nicotine content, NNC) or 0.4 mg nicotine/g tobacco (VLNC), both with tar yields of 9 ± 1.5 mg. Cigarettes are available in both menthol and non-menthol versions and participants will be assigned the flavor that they prefer based on their usual menthol preference.

b. **Advertising & Recruitment:** We will contact schools to receive permission to set up informational tables during lunchtime that will provide information about the study. Interested adolescents will be read a short script with information about the study and if they remain interested will be screened for eligibility. We will also advertise the study on regional buses, in local and school newspapers, on Craigslist.org, on Facebook and Instagram, on the Center for Alcohol and Addiction Study's (CAAS) website, other places online and on social media, via direct mail, and at local events. To reach adolescents outside of high school, we will also promote the study at GED classes and youth job training programs, and/or social service agencies such as community action programs, using flyers and information sessions. Interested adolescents can self-administer a screening interview via iPad, provide contact information to receive a follow up phone call, or call the research office to complete a brief, confidential telephone screening interview to establish eligibility.

c. **Phone Screen (Provided as attachment):** The screening questionnaire will query past 6-month cigarette use, past 30-day frequency of other tobacco/nicotine, alcohol, and other drug use, motivation for smoking cessation, and other items required to establish preliminary eligibility (see Adolescent Phone Screen). The screening will remain the same whether or not it is administered via iPad or over the phone. The screening questionnaire is used only to determine eligibility and will not be used as research data.

d. **Informed consent procedure:** Adolescents who meet initial eligibility criteria, and who remain interested after hearing a more detailed description of the study, will provide contact information for their parent or legal guardian (minors only) so that parental informed consent can be obtained; 18-19 year olds can provide their own informed consent (see **18+ Consent** attachment). Research staff will call the minor's parent/guardian and provide the study information and answer any questions that they have (see **Parent Phone Script** attachment). If parents are willing to consent to their child's participation, we will mail or email them a consent form to sign (and one to keep), which the adolescent participant will bring to the first session (see **Parental Consent** attachment). Eligible interested adolescents (with verbal parental consent if minors) will be scheduled for the initial in-person session and transportation arranged if necessary (see **Adolescent Assent** attachment).

4. Screening

a. During the initial in-person screening, participants will complete several questionnaires and have their CO taken to confirm eligibility to enroll. Female participants will also submit a urine sample to test for pregnancy. Urine will be sampled for cotinine levels if necessary. The Timeline Follow back, stages of change, and MINI suicide subscale will be used to determine eligibility. We estimate that we may need to consent up to 200 adolescents to result in a final sample of N=120.

b. <u>Inclusion Criteria</u>

1) Ages 15~~-19~~ 20 inclusive
2) Male and female current daily smokers
    a. Defined as self-reported daily cigarette smoking at phone screening AND

   b. a breath carbon monoxide (CO) criterion of 5 ppm or higher; if this is not met, urine cotinine levels, detected by a NicAlert cotinine screening device, must indicate recent smoking (level 3 or higher)
3) Current users of alternative tobacco product(s)
   a. Defined as any self-reported use of at least one non-cigarette tobacco product (e.g., e-cigarettes, little cigars, cigarillos, hookah, etc.) in the past 30 days
4) Participants must speak and comprehend English well enough to complete study procedures.
   a. Participant will be asked to read aloud first few lines of informed consent and then summarize the contents aloud to check for competency

Exclusion Criteria

1) Unwilling to use research cigarettes as part of the study
2) Self-reported ~~binge drinking of alcohol (≥ 4/5 drinks within a 2-hour period for female/male participants respectively) or use of illicit or non-prescribed drugs (excluding marijuana) ≥ 10 days in the past 30 days~~daily use of alcohol
   a. We will ask about daily alcohol and drug use in the phone screen, and we will use the Timeline Follow-Back to assess current and recent marijuana and alcohol use.
3) Currently seeking treatment to quit smoking, and/or intending to quit smoking for good in the next 30 days
   a. This information corresponds to questions 2 & 3 of the Stages of Change measure which will be administered at the in-person screening.
   b. These participants will be excluded, and provided with referral information for cessation services in the community.
4) Suicidal ideation in the past month or any past-year suicide attempts
   a. Suicidal ideation determined by the MINI suicide subscale at the in-person screening (Questions 4 and 5)
   b. Suicide attempt in the past year determined by MINI question 6.a. (If participant has a lifetime history of suicide attempt between 1 and 10 years ago, licensed medical monitor approval required)
   c. If a participant indicates that he/she currently has suicidal ideation during this or any future session, the Emergency Protocol will be followed in which a Licensed Clinician will be contacted immediately, and participants will speak with the clinician over the phone and the clinician will determine the appropriate action to take to keep the child safe.
5) Pregnant or breastfeeding
   a. Determined by urine test at in-person screening; tested again at each in-person visit; participant will be excluded or withdrawn if test indicates pregnancy
   b. Self-reports current breastfeeding at in-person screening
6) Any medical or psychiatric conditions in which participation is likely to pose a significant threat to health or for which the condition could interfere with the ability of the participant to fully participate (as determined by LMP).
7) Having participated in another research study during the past year in which they were switched to research cigarettes for longer than one week.

Initial eligibility determination will be made by the RA based on the above criteria. If the participant is deemed initially eligible, the BL1 session will immediately being. Eligibility

criteria will be reviewed by the medical monitor (Dr. Cioe) and the PI to confirm final eligibility for the study prior to randomization (BL2).

5. **Baseline 1 Session**
    a. **Purpose:** If the participant is eligible after screening procedures, the first baseline session (BL1) will immediately begin. Participants who are ineligible will be paid $25 and will not complete the BL1 procedures. The RA will make the initial determination of eligibility; final eligibility will be confirmed by the study clinician and PI prior to BL2 (randomization).
    b. **Procedure**: BL1 will consist of an initial battery assessing baseline characteristics (see measures schedule). After these assessments, participants will be oriented to the EMA procedures. Research staff will help participants download the app to their smartphones, and then train them on how to complete the assessments. EMA surveys will begin the next day (see **Table 2** and section on **EMA Procedures** below). During the 1-week baseline EMA period, participants will be instructed to smoke and use other tobacco products as they normally would.
6. **Baseline 2 (BL2) Laboratory Session**
    a. **Purpose:** During this session, participants will be randomized to their study cigarette. Using multiple laboratory-based measures, this session establishes the acute effects of study cigarettes on craving, withdrawal symptoms, and subjective reinforcement value of the participant's randomly assigned study cigarette.
    b. **Procedure:** At the beginning of the session, participants will provide a breath CO sample, complete a timeline follow-back measure for the interim week (i.e., between BL1 and BL2) which will query their use of cigarettes, alcohol, marijuana, and alternative tobacco products, complete a delay discounting task, and complete measures of craving (QSU), withdrawal (MNWS) and mood (PANAS). They will then smoke one study cigarette in the laboratory (while being observed by a research assistant in an adjoining room). Female participants will also provide a urine sample for a pregnancy test. Next, they will provide a post-smoking CO sample, repeat the QSU, MNWS, and PANAS, and then complete measures of cigarette subjective effects (CES), and perceived health risks of smoking. Then, they will complete a cigarette purchase task (CPT), a behavioral economics-based measure of cigarette reinforcement, which assesses hypothetical demand for cigarettes across a range of prices. They will complete the Experimental Tobacco Marketplace task which is described in detail under the Measure section. Participants will also complete a Health Changes Questionnaire to assess any adverse events. Participants will also complete an objective assessment of respiratory function using a Spirometer to measure their breath volume, and then provide urine samples for biomarker assessment.
    c. **Product Dispensing:** Participants will be randomized to switch from smoking their usual brand cigarettes to smoking either NNC or VLNC cigarettes over a subsequent four-week experimental period. After all BL2 assessments are completed, study cigarettes will be dispensed to the participant at 125% of their weekly (between BL1 and BL2) consumption of cigarettes. Extra cigarettes are provided, as is typical in studies of this type (e.g., Donny et al., 2015; Hatsukami et al., 2010), to accommodate potential increases in smoking that may occur, and to allow any compensatory smoking (e.g., with VLNC cigarettes) to be detected. Participants will be instructed to smoke only the research cigarettes provided to them by the study rather than their usual brand cigarettes or any other cigarettes. They will also be told that they may choose to use

other nicotine-containing products (not provided by the study), such as e-cigarettes and little cigars, during the study. This distinguishes the proposed trial from past work with adolescents, which excluded most poly-tobacco users and prohibited non-cigarette product use during the experimental period. Participants will be dispensed cigarettes for a ~~7~~14-day period~~; however; if their session is scheduled earlier or later (e.g., due to school holiday or vacation), then the RA may dispense up to a 14-day supply.~~. Participants will also be informed that if they run out of study cigarettes prior to their next scheduled visit, they can schedule a time to pick up more at an Unanticipated Visit, which will follow the same visit protocol as W1/W3 Check-In Visit. If such an Unanticipated Visit occurs, the RA will dispense product for the number of days until their next scheduled visit (e.g., if they have two days until their next visit, then the RA will dispense two days' worth of study product).

d. **Product Compliance and Accountability:** Participants will be required to keep track of all the cigarettes provided to them. Each week, they will return all unused cigarettes and empty or unopened cigarette packs to the research staff, and will receive incentives for doing so. Participants will be asked if they have decided to quit smoking at each lab visit. If they wish to quit, they will be asked if they still want to receive study cigarettes. If not, no cigarettes will be dispensed. The participant will be retained in the study with no penalty and will continue to complete all subsequent EMA and other self-report assessments. In an ongoing study (IRB#1404001032), we dispense research cigarettes in this manner to 15-19-year-old daily smokers with approvals from the FDA, Brown University IRB and permission (waiver) from the Rhode Island Attorney General (K01CA189300, PI Cassidy). We are in the process of obtaining such a waiver for the current study as well. We will provide incentives for study cigarette accountability, which we have found to increase study cigarette compliance in our prior trials. The incentive will be a payment at each in-person session, which encourages participants to keep track of their study cigarettes, minimizes hoarding of study cigarettes, and discourages sharing of study cigarettes with other people. The payment schedule for returning unsmoked cigarettes is as follows: 50-74% returned, $5; 25-49% returned, $2.50; and 0-24% returned, $0. Returned empty packs will receive $1. At each session, participants will be reminded that if they do not like their study cigarettes, they can use alternative products that are not cigarettes, as the goal of the study is to model a scenario in which a nicotine reduction policy applies only to cigarettes. Honest reporting will be encouraged throughout the study. The total possible incentive for cigarette/empty pack return is $5.

e. **Randomization:** Using procedures similar to our current study, a double-blind randomization procedure will be used. We will stratify on the following four variables to optimally balance conditions on factors that might influence responses to study cigarettes:
    a) Gender
    b) Average cigarettes per day in past month (CPD; < 8 cigarettes vs. > 8 cigarettes)
    c) frequency of past-month alternative combustible tobacco product use (< 10 days vs. > 10 days).
    d) frequency of past-month non-combustible tobacco product use (< 10 days vs. > 10 days).

Each participant will be assigned a randomization code which will be associated with blind codes for cigarette cartons. The research assistant dispensing the cigarettes to each participant will be blind to the cigarette nicotine content, and will dispense cigarettes based on the blind code linked to each individual's randomization code. The randomization schedules and the link between the randomization code, blind codes and treatment assignment will be maintained securely by the CAAS Data Core (Suzanne Sales and Tim Souza).

f. **EMA Platform**: All EMA assessments will be conducted via a smartphone app designed for this purpose, PiLR EMA (MEI Research, Edina, Minnesota; http://pilrhealth.com/), which was developed and made available by MEI Research, Inc. The app is fully customizable for conducting time-based, event-based, contingent and random surveys, and supports logic branching to ask follow-up questions only when certain events are noted. The app uses a cloud-based infrastructure to store data securely, and this software has been used successfully in other smoking studies conducted here in vulnerable populations (Allen, Tosun, Carlson, & Allen, 2017) and in ongoing research on other health behaviors at our Center (for further information about ongoing behavioral health projects using the app, see http://pilrhealth.com/projects/). The app uses a mobile-friendly interface to capture data, including options for 'slider' visual analog scales (VAS) to input Likert scale items, text-based data entry, and check boxes to indicate the presence of certain environmental features. The app will be downloaded onto participants' phones at the BL1 session. As we have done in prior EMA studies, if participants do not have a smartphone, they will be loaned one for the duration of the study. Further detailed information about the security and data transmission of the app are included as an attachment to this protocol. During the BL1 session, participants will be given detailed instructions on how to use the app, including information on when the app will notify them to complete a survey and when they should initiate a survey themselves (e.g, after each cigarette or use of any other tobacco product). Participants will be provided with a 'hotline' phone number to call for general questions and technical support. Further information about app data safety and confidentiality is included as an attachment.

g. **EMA Procedures**: Each assessment will take approximately 90 seconds to complete. EMA report types will include: 1) Interval-contingent wake-up reports whereby participants will be signaled to record the number of cigarettes and other nicotine and tobacco products they used the day before; 2) Event-contingent tobacco use reports wherein participants will initiate a report each time they smoke a cigarette or use an alternative tobacco product; each such report will query social context, withdrawal, mood and other factors; and 3) Signal-contingent random prompts whereby adolescents respond to an app-initiated audible signal which will prompt a report with the same questions as the event-contingent tobacco use report to determine non-tobacco levels of mood and other factors for comparison purposes. Random prompts will be signaled 4 times per day, once per 3-hour block: 8am-11am; 12pm-3pm; 3-6pm; 4-7pm, 8-11pm] The purpose of the random prompts is to assess non-tobacco levels of withdrawal, craving, and other variables in order to compare these with the variables reported during tobacco reports. Variables such as mood, ~~location~~ sett and peer context will be included as these may also affect adolescent smoking and can be explored as potential moderators of effects. Random prompts will also ask participants if they smoked cigarettes or used any other tobacco products since their last

report, and if so, they will be prompted to record it in order to capture any missed product use. The minimum number of surveys to be completed per day is five (one interval-contingent morning report and four random prompts). Cigarette reports can be compared directly with reports on other forms of tobacco to identify common and unique antecedents, and contextual factors for use of each type of product use can be compared to those during random prompts. During Weeks 2 and 3, to reduce participant burden, only the morning report will be required. The **schedule of EMA assessments and question wording is included as an attachment**.

7. **Week 1 Safety & Product Dispensation Check-In**
    a. **Purpose:** This check-in visit can occur either at our research lab or in the community at the participant's preference and convenience. The purpose of this check-in is to check on safety/any adverse events, ~~check CO level~~, and dispense product; allowing participants to meet us in the community will help reduce the burden of travel time for participants and is designed to reduce study attrition, particularly among participants for whom the logistics of scheduling and transportation may be challenging.
    b. **Procedures:** Participants will ~~provide breath C~~O, complete a timeline follow-back measure for the interim week which will query their use of study and non-study cigarettes, alcohol, marijuana, and alternative tobacco products. Participants will also complete a Health Changes Questionnaire to assess any adverse events, and the RA will follow-up on any ongoing medical events. Note: These sessions were conducted virtually post-COVID.
8. **Week 2 Laboratory Session**
    a. **Purpose:** This laboratory session will evaluate mid-point responses to study cigarettes.
    b. **Procedures:** At the beginning of the session, participants will provide a breath CO sample, complete a timeline follow-back measure for the interim week which will query their use of study and non-study cigarettes, alcohol, marijuana, and alternative tobacco products, and complete measures of craving (QSU), withdrawal (MNWS) and mood (PANAS). Female participants will provide a urine sample for a pregnancy test. They will then smoke one of their study cigarettes. Next, they will provide a post-smoking CO sample, repeat the QSU, MNWS, and PANAS, and then complete measures of cigarette subjective effects (CES). Participants will also complete a Health Changes Questionnaire to assess any adverse events, and the RA will follow-up on any ongoing medical events.
9. **Week 3 Safety & Product Dispensation Check-In**
    a. **Purpose:** As described above (Week 1 Check-In), this check-in visit can occur either at our research lab or in the community; the purpose is to check on safety/any adverse events, ~~check CO~~, and dispense product.
    b. **Procedures:** Participants will ~~provide breath CO~~, complete a timeline follow-back measure for the interim week which will query their use of study and non-study cigarettes, alcohol, marijuana, and alternative tobacco products. Participants will also complete a Health Changes Questionnaire to assess any adverse events, and the RA will follow-up on any ongoing medical events. Note: These sessions were conducted virtually post-COVID.
10. **Week 4 Session**
    a. **Purpose:** This laboratory session will evaluate end-point responses on behavioral economic measures and allow for collection of final biomarkers and cigarette collection.

b. **Procedures:** At the beginning of the session, participants will provide a breath CO sample, complete a timeline follow-back measure for the interim week which will query their use of study and non-study cigarettes, alcohol, marijuana, and alternative tobacco products. Female participants will provide a urine sample for a pregnancy test. Then, they will complete the cigarette purchase task (CPT), a behavioral economics-based measure of cigarette reinforcement, which assesses hypothetical demand for their usual brand and study cigarettes across a range of prices. Finally, they will complete the Experimental Tobacco Marketplace task again. Participants will also complete a Health Changes Questionnaire to assess any adverse events, and the RA will follow-up on and close any ongoing medical events. Should any adverse events be left open at this time, they will be re-assessed at the 30-day call. Participants will also complete an assessment of respiratory health and provide urine samples for biomarker assessment. Participants will also administer and anonymous debriefing survey which will ask them about the honest of their reporting. At the end of the week 4 session, following return of all products, participants will be debriefed on products used during the study. Health risk information will be presented for combusted cigarettes, e-cigs, and other tobacco products, using a handout drawn from CDC Fact Sheet.

~~b.~~c. **Post-**Session COVID survey and qualitative interview: Following the last sessions, participants will be asked if they would like to participate in a short survey and interview. They will first complete a brief survey of their COVID-19 experiences. Then, the researchers will conduct a recorded qualitative interview about their experiences with the EMA app in order to improve future app use.

11. **Outcomes, Measures Justification, Descriptions, and Schedule**

Primary Outcomes

- Cigarettes smoked per day
- Amount of total alternative product (ATP) use

Secondary Outcomes

- Amount of combustible and amount of noncombustible ATP use
- Toxicant exposure (total nicotine equivalents and NNAL)
- ~~FEV outcomes~~

Exploratory Outcomes

- ATSQ score
- Perceived Health Risk Questionnaire
- Nicotine dependence score
- Differences in craving across time and product type
- Differences in withdrawal across time and product type
- Measures of reinforcing efficacy/cigarette demand from the Cigarette Evaluation Scale
- Hypothetical Purchasing in the Experimental Tobacco Marketplace

a. **Background/Descriptive Measures**: A modified version of the **PATH Demographics and Tobacco Use History** (Adolescent version) will be used to assess participant characteristics and lifetime history of tobacco product use (using a comprehensive list of combusted and non-combusted products), including ages of initiation and progression through smoking milestones such as daily use. The Vaping History Questionnaire will be used to assess lifetime use of e-cigarettes, including e-cigarette characteristics. **Social and Environmental Influences** (tobacco use by parents and peers; perceived norms for cigarettes and e-cigs) will be assessed using a modified Interpersonal Influences Questionnaire (Colby et al., 2005. We will use the reliable and valid **Smoking Stage of Change** (Velicer, Hughes, Fava, Prochaska, & DiClemente, 1995) to assess readiness to change at baseline and week 4. The **Center for Epidemiological Studies-Depression Sca**le (CES-D; Radloff, 1991) is a widely used and validated 20-item questionnaire assessing depressive symptoms in the past week. This measure will be used for sample description given the high co-occurrence of smoking and depression. Respiratory symptoms will be assessed using the **American Thoracic Society Questionnaire** (ATSQ; Comstock, Tockman, Helsing, & Hennesy, 1979). Participants report the frequency of experiencing each of 8 respiratory symptoms (e.g., morning cough, wheezing, shortness of breath when walking). We recently validated this scale for assessing the severity of respiratory symptoms associated with smoking in adolescents (Cassidy, Roberts & Colby, 2015). **Nicotine Dependence** will be assessed using the modified Fagerstrom Tolerance Questionnaire (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Scores on this measure will be evaluated as an outcome at Week 4 as an index of changes in dependence as a function of VLNC exposure.
b. **Safety:** Pregnancy tests will be performed for all female participants at Screening/BL1, BL2, and both lab visits (weeks 2 and 4). The **suicide subscale** from the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 2010) will be used at Screening to evaluate suicide risk. CO level will be obtained at every session to evaluate level of exposure to smoke; a large increase in CO (i.e., CO > 80 ppm) can be a reason for withdrawing a participant from the study. **Brief Medical History** (Screening/BL1) assesses physical and emotional health to establish eligibility for participation (determined by the medical monitors). In subsequent sessions, the **Health Changes Questionnaire** asks whether the participant experienced any changes in his/her physical or emotional health since their last visit, including whether they have visited the doctor, the hospital, or whether they have had a change in any of their medications. Any endorsement of a negative health change will be tracked as an adverse event.
c. **Frequency of tobacco and other drug use measures**: Past 30-day tobacco product use will be comprehensively assessed using a **Timeline Follow-Back (TLFB)**, a reliable calendar-assisted interview validated for estimating daily use of tobacco and other substances in adolescents (Lewis-Esquerre et al., 2005). The TLFB will determine: # cigarettes per day; frequency of e-cig use (including nicotine concentration in e-liquid) and use of all other tobacco products; use of alcohol (# standard drinks/day); and frequency of marijuana use and other illicit or recreational drug use. The TLFB will also be used to assess tobacco, alcohol, marijuana and other drug use between sessions to evaluate use over the course of the study.
d. **Biomarkers. Expired breath CO** level is a reliable and valid assessment of recent smoking and will be measured using a Vitalograph CO Monitor. CO will be assessed at BL to confirm

smoking status and for sample description. CO will be evaluated pre- and post-cigarette in each labs session, and as an outcome at Week 4 as a biomarker of changes in effects of changes in combustible product use. Urine samples will be analyzed for the tobacco-specific nitrosamine 4-methylnitrosamineo-1-(3-pyridyl)-1-butanol (**NNAL**), a biomarker of tobacco smoke carcinogen that decreases upon combustible tobacco cessation or reduction (Benowitz et al., 2012; Hecht et al., 2014) and total nicotine equivalents (**TNEs**), which is a measure of total nicotine exposure (i.e., from all nicotine-containing products). Both TNEs and NNAL will be analyzed from samples collected at baseline (BL2) and at the end of the product use period (W4). Samples will be shipped twice per year for analysis to the University of Minnesota and will be analyzed by Sharon Murphy, Ph.D. (see letter of support included in grant application). Scores on this measure will be evaluated as an outcome at Week 4~~. Forced Expiratory Volume (**FEV**) is a measure of how much air a person can exhale during a forced breath. Cigarette smoking is associated with reduced lung function in adolescents, indicating mild airway obstruction, and with slowed lung growth during adolescence (Gold et al., 1996) whereas quitting smoking leads to improvement in lung function and slows reductions in lung function associated with aging in later adulthood (Kohansal et al., 2009). Forced vital capacity (**FVC**) is the total volume of breath exhaled during the test; FEV1 is the volume exhaled within the first second. FEV will be measured with a water-filled recording spirometer. Research assistants will be trained by Co-Investigator Cioe, who has experience measuring FEV in clinical settings, to take these measurements. Each participant will perform three forced expirations; FVC and FEV1 means will be calculated for each expiration judged acceptable by the RA.~~

e. **Assessments of Potential Mechanisms.** The **Brief Questionnaire on Smoking Urges** (Brief QSU; (Cox, Tiffany, & Christen, 2001) assesses craving for cigarettes. Factor 1 assesses desire to smoke/positive reinforcing aspects of smoking, and Factor 2 assesses relief from withdrawal/negative reinforcing aspects of smoking. The **Minnesota Nicotine Withdrawal Scale** (MNWS; Hughes & Hatsukami, 1986) asks individuals to rate their experience of withdrawal from nicotine using a four-point scale across 7 items reflecting DSM-IV criteria for nicotine withdrawal syndrome. **The Positive and Negative Affect Scale** (PANAS; Watson, Clark, & Tellegen, 1988) asks participants to rate how they are feeling at the moment, using a series of adjectives, on a 5-point scale (from "not at all" to "extremely"); its items form two factors tapping positive affect and negative affect. All of these measures have been validated for use in adolescent smokers and shown to be sensitive to smoking abstinence effects (Colby et al., 2010) and effects of VLNC cigarettes (Kassel, Evatt, et al., 2007). Each participant will rate how much he/she enjoyed the cigarette they just smoked using the **Cigarette Evaluation Scale**, which assesses subjective characteristics such as enjoyment on a 7-point Likert scale (CES; (Arger et al., 2017; Cappelleri et al., 2007). Participants will report their perceptions of the health risks associated with both their usual brand and their study cigarette brand using the **Perceived Health Risks Assessment** (Hatsukami et al., 2010).

f. **Behavioral Economic Assessments of Reinforcing Efficacy.** The **Cigarette Purchase Task** (Jacobs & Bickel, 1999; MacKillop et al., 2008) will be used to assess demand for both their usual brand cigarette which may change as a function of VLNC exposure (Smith, et al., 2016). Participants will be asked how many cigarettes of their usual brand and their study cigarette they

would purchase per day at increasing costs per pack, starting with how many they would consume when cigarettes are free (zero price). This measure has been validated for use in adolescents in a study directed by primary mentor Colby (Murphy, MacKillop, Tidey, Brazil, & Colby, 2011). Participants will also complete the CPT for their study cigarette. Similarly, the Juul Purchase task will be administered to those participants who report past 30-day Juul use..

Delay discounting is a measure of impulsivity which asks participants to make hypothetical choices between a fixed amount of money now and larger amount of money after a delay. This measure has been widely used in substance abuse research, and correlates with smoking status in adolescent smokers (Quisenberry et al., 2016) and is included for descriptive and exploratory purposes. The **Experimental Tobacco Marketplace** (Bickel et al., 2018) will be used to assess effects of cigarette price on consumption of cigarettes and alternative products. In the task, participants are shown a virtual marketplace of tobacco products, including both noncombustible and combustible alternative products, as well as cigarettes. Participants are instructed to make hypothetical purchases of tobacco products that they would use for the week. Participants are given an experimental budget of money which can be used in the marketplace and are instructed that they can 'save' unspent money. The costs for the other products will reflect average prices in RI and will not change across conditions. For each iteration of the task, participants will receive account balances approximately equal to the money they would spend on three days' worth of tobacco. They can purchase as many or few tobacco products as their account balance allows (only packaged products, e.g., whole cigarette packages, can be purchased). For example, if a participant smokes a pack of cigarettes each day, then she is spending ~$10.00 per day on tobacco, as this is the price of a pack of cigarettes in RI. During each iteration of the ETM task, she will have an account balance of $30.00 to spend on tobacco for a 3-day period. The hypothetical cigarette available will be their study cigarette. Across trials, the price of cigarettes increases while the prices of alternative products remain the same. On each trial, participants can choose to purchase any combination of tobacco products that they choose, as long as they stay within their experimental budget. Across four trials, the price of cigarettes will increase ($0.12, $0.25, $0.50, ~~and~~ $1.00, $2.00, $4.00, $8.00, and $16.00 per cigarette). The following tobacco/nicotine products will be available on the ETM:

a) Study cigarettes – menthol OR non-menthol flavors depending preference;
b) Little cigars (e.g., Winchester, Cheyenne) – menthol and tobacco flavors;
c) Cigarillos (e.g., Black and Mild; Swisher Sweets) – menthol and tobacco flavors;
d) E-cigarettes (e.g., cigarette-like systems such as Juul and tank-like systems such as NJOY prefilled tanks) – menthol and tobacco flavors;
e) Snus (e.g., Camel and Marlboro snus) – menthol and tobacco flavors;
f) Conventional smokeless tobacco products (e.g., Copenhagen) – menthol and tobacco flavors;
g) Non-prescription medicinal nicotine (e.g., 2mg and 4mg nicotine gum; 7, 14 and 21 mg nicotine patch) – menthol and regular flavors;

This task will first be administered at Baseline 2 following acute cigarette exposure to assess intentions to purchase alternative products following initial exposure to study cigarettes, and at Week 4 to assess effects of extended exposure to study cigarettes on intentions to purchase

alternative products across groups. This measure will be compared with patterns of product use generated from EMA assessment in the field.

g. Laboratory Measures schedule (Table 1)

Measure	Screening	Baseline 1	Baseline 2	Week 1	Week 2	Week 3	Week 4
Demographics/Tobacco Use History and Exposure	X						
Brief Medical History	X						
Smoking Stages of Change	X						X
MINI Suicide Subscale	X						
Pregnancy Test	X	X	X	~~X~~	X	~~X~~	X
Timeline Follow Back (TLFB)	X		X	X	X	X	X
Breath Carbon Monoxide	X		X	~~X~~	X	~~X~~	X
Dependence (mFTQ)		X			X		X
ASTQ Respiratory Questionnaire			X		X		X
Delay Discounting		X					X
Environmental Tobacco Smoke/Social Influences		X					
Depressive Symptoms (CESD)		X					
Quit Intentions Questionnaire			X	X	X	X	X
Health Changes Questionnaire			X	X	X	X	X
Craving (Brief QSU) (pre/post cig)			X		X		
Withdrawal (MNWS) (pre/post cig)			X		X		
Affect (PANAS) (pre/post cig)			X		X		
Cigarette Evaluation Scale (post cig)			X		X		

Perceived Health Risks (UB)	X		
Perceived Health Risks (Study)	X		X
Cigarette Purchase Task (UB)	X	X	X
Cigarette Purchase Task (Study)	X	X	X
Juul Purchase Task	X	X	X
Experimental Tobacco Marketplace	X		X
~~**Respiratory Health Outcomes (FEV)**~~	~~X~~		~~X~~
Urine NNAL/TNEs	X		X
Debriefing Questionnaire			X

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12. **30-Day Follow Up Call:** Participants will be contacted after 30 days by telephone to assess current tobacco use, quit status, and to assess overall safety. Participants who have not quit will be advised to do so.
13. **Compensation:** The following payment schedule for in-person session attendance will be used:
    a. $25 for BL1; $50 for BL2; $15 each for W1 and W3, $50 each for W2 and W4. If a participant comes in for the in-person screening but is ineligible, they will still be paid $25 for their time provided they meet the CO or NicAlert inclusion criteria. Participants will be paid $~~2~~5.00 per day that they ineracted with the phone accorign to the intrsucrions given in Weeks 1, , and 5; in Weeks 3 and 4, they ~~that they~~can complete ~~at least~~ one EMA assessment for $2.00 daily for a possible maximum total of $173~~70~~. ~~A completion bonus of $75 will be given to participants who attend all laboratory sessions.~~ A bonus payment of $50 will be paid to participants who complete 80% or more of their EMA surveys. Participants will be eligible to earn up to $40 in random bonuses if they interact with the app A completion bonus of $75 will be given to participants who attend all laboratory sessions. A maximum of $20 possible compensation is available for returned cigarettes. Bonus payments are included because study procedures involve considerable time commitments and five sessions, thus attrition is a potential issue. Participants are free to discontinue at any time and will receive full compensation for the sessions they complete. The total possible compensation will be $523~~420~~. Participants will be paid using ClinCard.

14. Risks and Benefits. **Potential risks and benefits for participants**

a. Subjective discomfort (survey questionnaires): The protocol includes survey questions about medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could make the participant feel uncomfortable. However, the questions we ask are commonly used

in research and clinical practice and the participant will not be required to answer any question he/she is not comfortable answering. Answers to these questions will be kept confidential.

b. Subjective discomfort (biological samples): The participant may feel some discomfort about providing breath and/or urine samples for analysis. This probability of this risk is low, based on our past experience using these measures. Interactions with participants will be conducted in private rooms. Urine sample collection is private (i.e., unsupervised); the participant will provide the sample in a private bathroom within the laboratory suite. Discomfort will be further minimized by employing trained staff to conduct all procedures and emphasizing that study participation is voluntary.
c. Breach of Confidentiality: A risk of the interview is loss of privacy if other people find out the results. We will work to ensure that the participant's confidentiality is kept. Research data without identifiers will be maintained in a locked file cabinet and on password-protected computers in the research staff workplace, with only code numbers identifying participants. Study consent forms and the linkage between the participants' names and codes will be stored in a locked file cabinet in the Contact PI's office, on a separate floor of the building.
d. Smoking Cigarettes: The participant will smoke a single cigarette in the laboratory on 2 separate occasions. Study participation is restricted to established daily smokers so that this limited exposure will present no increased risk of harm than their current smoking status incurs.
e. Smoking Withdrawal: The participant may experience some discomfort related to nicotine withdrawal as a function of switching to VLNC cigarettes over an extended period. Symptoms can include irritability, frustration, anxiety, depressed mood or sadness, desire or craving to smoke, difficulty concentrating, and increased appetite or hunger. These feelings can be uncomfortable but they are normal, temporary, and usually mild. Participants are not prohibited from using other nicotine-containing products, which would prevent or reduce these symptoms.
f. Coercion: Coercion is a possible risk due to monetary compensation for participation; however, the likelihood of this risk is low because the compensation is commensurate with time and effort required for this study.
g. Compensatory smoking: The possibility exists that use of VLNC cigarettes over an extended period may lead to compensatory smoking (i.e., more intense or frequent smoking in an attempt to derive more nicotine from study cigarettes). However, research to date indicates that this outcome is unlikely. We will monitor the participant's weekly cigarette use and CO levels to evaluate the extent to which compensatory smoking is occurring, and will make changes to the protocol to reduce this as necessary.
h. Lower perceived risk of harm: The possibility exists that use of VLNC cigarettes over an extended period may lead to perceiving a reduced risk associated with VLNC cigarettes; we will debrief the participant post-study on risks associated with smoking. All cigarettes are harmful to a person's health. Smoking can lead to severe or fatal medical problems including heart disease, respiratory (breathing) problems and diseases, cancer, diabetes, and other health risks. The study cigarettes do not provide less risk than the participant's usual brand cigarette.

15. Adverse Events

a. Collection and reporting of AEs and SAEs

While participating in the trial, adverse events and changes in medications will be assessed at every study visit and carbon monoxide will be obtained. Medical events will typically be

identified during the administration of the Health Changes Questionnaire. Other events may be identified by spontaneous reports during non-scheduled assessments.

b. <u>Questionnaire items that will be reviewed:</u>

<u>Health Changes Questionnaire</u>

1) Have you noticed that your physical health or mental health have gotten worse since your last visit? If Yes, please describe.

2) Have you had any changes in medication since your last visit? If Yes, please describe:

3) Since your last visit, have you gone to the doctor? If Yes, please describe:

4) Since your last visit, have you gone to the hospital? If Yes, please describe:

No new AE required if one or more conditions below are met and the description does not otherwise meet the definition of an AE.

1) Existing AE already open for reported symptom
2) Pre-existing condition without increase in severity or frequency of symptoms (brief medical history will be updated if not previously reported).
3) Received preventative or follow-up medical care.
4) Other (explain).

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

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

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

1) Expired breath Carbon Monoxide >80 ppm
2) Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will

be reviewed by the MPIs and medical monitor to determine whether continued participation in the study is appropriate.

3) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then an MPI can withdraw him/her from the study at her discretion.

Serious adverse events (SAEs): Information about all serious adverse events will be collected and recorded on a standard Serious Adverse Event Report Form. To ensure participant safety, each study-related serious adverse event will also be reported to the IRB office within 72 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1.is fatal or life-threatening

2. requires or prolongs hospitalization

3. results in persistent or significant disability/incapacity

4. constitutes a congenital anomaly or a birth defect

5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A hospitalization would not be considered to be a serious adverse event if it was elective, pre-planned, or for a pre-existing condition that did not worsen since starting the study; or for treatment on an outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Any SAE occurring after the participant has signed the informed consent and until the participant has stopped study participation must be reported. Investigator responsibilities for notification of SAEs are described above.

c. Management of SAEs and Other Study Risks

The medical monitor will review all AEs. A study participant may be discontinued from the study if a medical monitor and/or an MPI determines it is the best decision in order to protect the safety of a participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an AE/SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes. Any AE that remains open will be reviewed and closed during the 30-day follow-up phone call.

d. Medical Monitor Contact information:

Robert Swift, M.D., Ph.D.

Email: robert_swift_md@brown.edu

Phone: 401-863-6643

Patricia Cioe, Ph.D., R.N.P.

Email: patricia_cioe@brown.edu

Phone: 401-863-6638

16. **Research Involving Minors.** Adolescents who meet initial eligibility criteria during the phone screen, and who remain interested after hearing a more detailed study description, will provide contact information for their parent/guardian (minors only) so that parental informed consent can be obtained; 18-19 year olds can provide their own consent. Minors will not be scheduled without research staff first talking directly to a parent/guardian. Research staff will call the parent or guardian, describe the study, and answer any questions. Consent forms will be mailed or emailed to the parent (with a copy to keep/option to print for their records). Adolescents will then be scheduled for the initial in-person session and transportation arranged if necessary. The adolescent (if a minor) will bring the signed consent form to the in-person screening session, or the RA will ensure that the participants' parent has electronically signed the consent form. Participants will complete informed assent (minors)/consent at the in-person screening session. A researcher will review the assent/consent form in detail, review all study procedures, and answer questions. Participants will receive a copy of their consent/assent form. Participants over 18 will need to provide an ID that indicates their age in order to participate.

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
MR1						What time did you go to bed last night?	Enter hour (text entry)	
MR1A						What time did you wake up today?	Enter hour (text entry)	
MR1B						Please rate how well you slept.	1 Not well at all to 10 Very well (categorical)	
MR2						Think about the time since the last report you completed yesterday and when you went to sleep. Did you forget to enter any smoke reports?	0=No 1=Yes	If "Yes", proceed to MR2B. If "No", skip to MR3.
MR2A						What time did you last use tobacco?	1=15 mins ago 2=30 mins ago 3=45 mins ago 4=1 hour ago 5=2 hours ago 6=3 or more hours ago	
MR2B						What did you use? Select all that apply	1=Non-study cigarette 2=Study cigarette 3= E-cigarette/vape 4= Cigar/cigarillo (Black & Mild, Swisher Sweets) 5= Smokeless tobacco (chew, dip, snuff, snus) 6=Hookah 7=Pipe (tobacco)	
MR3						How many study cigarettes did you smoke yesterday?	Numeric (integer) entry (0-200)	
MR4						How many non-study cigarettes did you smoke yesterday?	Numeric (integer) entry (0-200)	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
MR5						Select all alternative tobacco products you used yesterday.	0=None 1= E-cigarette/vape 2= Cigar/cigarillo (Black & Mild, Swisher Sweets) 3=Smokeless tobacco (chew, dip, snuff, snus) 4=Hookah 5=Pipe (tobacco)	Each endorsed choice brings up data entry for quantity (6A-6E)
MR6A						About how many puffs of E-cigarette/vape do you think you took?	Numeric (integer) entry (0-200)	Show only if "E-cigarette/vape" is selected in MR5
MR6A1						Did you finish a Juul pod or refill your vape tank?	0=No 1=Yes	Show only if "E-cigarette/vape" is selected in MR5
MR6B						About how many cigars did you smoke?	Numeric (integer) entry (0-200)	Show only if "Cigar/cigarillo) is selected in MR5
MR6C						About how much smokeless tobacco did you use?	Text entry	Show only if "smokeless tobacco" is selected in MR5
MR6D						About how much hookah did you use?	Text entry	Show only if "hookah" is selected in MR5
MR6E						About how much pipe (tobacco) did you use?	Text entry	Show only if "pipe (tobacco)" is selected in MR5

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
	FR0A	RR0A				Have you used tobacco in the last 30 minutes?	0=No 1=Yes	If "Yes", proceed to R0B. If "No", proceed to R1.
	FR0B	RR0B				Did you do a smoke report?	0=No 1=Yes	If "Yes", proceed to R1. If "No", proceed to R0C.
	FR0C	RR0C				Please do a smoke report now.	(Instruction)	All – random survey end.
	FR1					Think about the time since you woke up this morning. Did you forget to enter any smoke reports?	0=No 1=Yes	If "Yes", proceed to FR1B. If "No", proceed to FR2.
		RR1				Think about the time since you last completed a report. Did you forget to enter any cigarette or tobacco reports?	0=No 1=Yes	If "Yes", proceed to R1B. If "No", proceed to R2.
	FR1A	RR1A				What time did you last use tobacco?	1=15 mins ago 2=30 mins ago 3=45 mins ago 4=1 hour ago 5=2 hours ago 6=3 or more hours ago	
	FR1B	RR1B				What did you use? (Select all that apply)	1=Non-study cigarette 2=Study cigarette 3= E-cigarette/vape 4= Cigar/cigarillo (Black & Mild, Swisher Sweets) 5= Smokeless tobacco (chew, dip, snuff, snus) 6=Hookah 7=Pipe (tobacco)	IF 3,4 OR 5 show FR1C/R1C (flavor Q)

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
	FR1C	RR1C				What flavor was your product?	1=Tobacco 2=Menthol/Mint 3=Fruit 4=Candy 5=Vanilla 6=Desserts/Sweets 9=Other	
						Think about how you are feeling ***right now***. Do you feel…	(NWQ header)	
	FR2	RR2				Desire or craving to smoke a cigarette?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR3	RR3				Angry, irritable, or frustrated?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR4	RR4				Anxious or nervous?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR5	RR5				Difficulty concentrating?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
	FR6	RR6				Impatient or restless?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR7	RR7				Hungrier than usual?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR8	RR8				Depressed?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR9	RR9				Happy?	0=Not at all 1=A little 2=Moderately 3=Quite a bit 4=Extremely	
	FR10	RR10				Stressed?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
	FR11	RR11				Bored?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
	FR12	RR12				Where are you now?	0 Home/Dorm 1 Other's Home/Dorm 2 Work/School 3 Party/Bar/Club 4 Public Place (Outside) 5 Public Place (Inside) 6 Car/Bus/Other Transportation 99 Elsewhere	
	FR12O	RR12O				You chose other location. Please describe where you are now:	Text entry	Show if 'Elsewhere' is selected in R12
	FR13	RR13				Who are you with? (Select all that apply)	1 Friend(s) 2 Parent(s) 3 Sibling(s) 4 Boy/girlfriend 5 Teacher 6 Co-workers 7 Other persons 0 No one, I was alone	
	FR14	RR14				Are any of these people using tobacco products? (Select all that apply)	1=Cigarettes 3=E-cigarette/vape 4=Cigar/cigarillo 5=Smokeless tobacco 6=Hookah 7=Pipe (tobacco) 0=No other people are using tobacco	Do not show if only 'No One' is selected in R13 (code 2 intentionally skipped "study cig" to keep values consistent with similar fields)

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
	FR15	RR15				What are you doing? (Select all that apply)	1 Drinking Alcohol 2 Using Marijuana 3 Using other Drugs 4 Socializing 5 Exercising/Walking/Sports 6 Studying/Reading/Working 7 Game/Movie/Video/TV/Music 8 Social Media/Texting/On Phone 9 Resting 10 Eating/Drinking 99 Other	
	FR15A	RR15A				You chose Eating/Drinking. What are you eating or drinking? Select all that apply.	1 Meal 2 Snack 3 Caffeine drink 9 Other beverage	Show if 'Eating/drinking' is selected in R15
					AR0	What type of product did you use	1= E-cigarette/vape 2=Cigar/cigarillo (Black & Mild, Swisher Sweets) 3=Smokeless tobacco (chew, dip, snuff, snus) 4=Hookah 5=Pipe (tobacco)	IF 1,2 OR 3 show AR1B (flavor Q)
			UR1	SR1	AR1	What time did you last use [PRODUCT]?	1=15 mins ago 2=30 mins ago 3=45 mins ago 4=1 hour ago 5=2 hours ago 6=3 or more hours ago	Should be piped text To replace [PRODUCT] from item AR0.

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
					AR1A	What flavor was your product?	1=Tobacco 2=Menthol/Mint 3=Fruit 4=Candy 5=Vanilla 6=Desserts/Sweets 9=Other	
						Think about how you felt ***just before*** *[SMOKED/VAPED/*you used tobacco]. Did you feel…	IF FIRST REPORT WITHIN A 2 HOUR BLOCK (i.e. the long survey); ELSE go to UT1/ST1/AT1	Should be piped text for [tobacco PRODUCT] from item AR0.
			UR2	SR2	AR2	Desire or craving to smoke a cigarette?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR3	SR3	AR3	Angry, irritable, or frustrated?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR4	SR4	AR4	Anxious or nervous?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR5	SR5	AR5	Difficulty concentrating?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
			UR6	SR6	AR6	Impatient or restless	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR7	SR7	AR7	Hungrier than usual?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR8	SR8	AR8	Depressed?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR9	SR9	AR9	Happy?	0=Not at all 1=A little 2=Moderately 3=Quite a bit 4=Extremely	
			UR10	SR10	AR10	Stressed?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR11	SR11	AR11	Bored?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR12	SR12	AR12	Where were you when you used tobacco?	0 Home/Dorm 1 Other's Home/Dorm	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
							2 Work/School 3 Party/Bar/Club 4 Public Place (Outside) 5 Public Place (Inside) 6 Car/Bus/Other Transportation 99 Elsewhere	
			UR12O	SR12O	AR12O	You chose other location. Please describe where you were:	Text entry	Show if _R12=Elsewhere
			UR13	SR13	AR13	Who were you with when you used tobacco? Select all that apply.	1 Friend(s) 2 Parent(s) 3 Sibling(s) 4 Boy/girlfriend 5 Teacher 6 Co-workers 7 Other persons 0 No one, I was alone	
			UR14	SR14	AR14	Were any of these people using tobacco products? (Select all that apply)	1=Cigarettes 3=E-cigarette/vape 4=Cigar/cigarillo 5=Smokeless tobacco 6=Hookah 7=Pipe (tobacco) 0=No other people were using tobacco	Do not show if 'No one' is selected in _R13
			UR15	SR15	AR15	What were you doing just before you used tobacco? Select all that apply.	1 Drinking Alcohol 2 Using Marijuana 3 Using other Drugs 4 Socializing 5 Exercising/Walking/Sports 6 Studying/Reading/Working	

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
							7 Game/Movie/Video/TV/Music 8 Social Media/Texting/On Phone 9 Sleeping 10 Eating/Drinking 11 Other	
			UR15A	SR15A	AR15A	You chose Eating/Drinking. What were you eating or drinking? Select all that apply.	1 Meal 2 Snack 3 Caffeine drink 9 Other beverage	Show if 'Eating/drinking' is selected in _R15
						Think about how you felt ***just after*** you used [tobacco].		Should be piped text for [tobacco PRODUCT] from item AR0.
			UR16	SR16	AR16	Did you feel a desire or craving to smoke a cigarette?	0=None 1=Slight 2=Mild 3=Moderate 4=Severe	
			UR17	SR17	AR17	Thinking about the [product] you just used. How pleasurable was your [product]?	0=Not at all 1=A little 2=Moderately 3=Quite a bit 4=Extremely	Pipe in text to replace [product] from item AR0. depending on product used.
			UR18	SR18	AR18	Thinking about the [product] you just used. How satisfying was your [product]?	0=Not at all 1=A little 2=Moderately 3=Quite a bit 4=Extremely	Pipe in text to replace [product] from item AR0. depending on product used.

Morning Report	First Random Prompt Report of the Day (FR)	Random Prompt Report (RR)	Usual Brand Smoke Report (UR)	Study Cig Smoke Report (SR.)	Alternative Product Report (AR)	Item	Response Format	Logic
MRT1	FRT1	RRT1	URT1	SRT1	ART1	Thank you for reporting this!	(Instruction)	End of all reports