PROTOCOL VERSION # AND/OR DATE: Version 1.27, November 30, 2020

Title: Addictive Potential of Little Cigars/Cigarillos in Dual Users: Effect by Flavor and Sex

Background:

A. **Importance of the Problem:** The use of multiple tobacco products (i.e., polyuse) poses a substantial health risk and barrier to cessation [1-6]. As of 2014, 37% of US adult tobacco users use more than one product [7]. The risk for polyuse is highest and increasing among young adults [8-11]. One of the most popular forms of polyuse is the dual use of cigarettes and cigars, specifically little cigars and cigarillos (LCCs) [8, 9, 11-15]. Since cigarette-like LCCs are labeled as cigars, tobacco companies are able to circumvent cigarette-specific regulations on price, pack size, and flavors to create an attractive, cheap, and easily accessible alternative or supplement to cigarettes [16, 17]. LCCs are highly similar to cigarettes in their size and shape, and come in a variety of flavors (e.g., fruit, dessert, alcohol) to attract young people and women [16, 18-21]. Consequently, dual users smoke more combustible products, inhale cigar smoke more deeply, and smoke cigars with a greater intensity than single product users [2, 22-26]. These smoking patterns have great significance for the risk ofmorbidity and mortality, nicotine exposure, and dependence, thus hindering cessation. Moreover, young adult polyusers are more likely to use alcohol and illicit drugs than cigarette-only users [8, 11].

LCCs are used for two primary reasons: their relatively lower cost and flavor offerings [21, 27]. They are less costly than cigarettes due to a lower tax rate and lack of minimum pack size requirements [16]. Young adults are more price sensitive to tobacco products than older adults [28-30]. Therefore, as cigarettes become more expensive, young adults may substitute with LCCs rather than quit or cut back to satisfy their nicotine addiction, thereby hindering public health cessation efforts. Flavors mask the harsh taste of tobacco, reduce throat irritation and make smoke easier to inhale, which increases nicotine intake, addiction, and carcinogen exposure [20, 31-34]. Moreover, taste sensitivity decreases with age, and women are more taste sensitive than men [35, 36]. Indeed, sensory effects are significant reinforcers of smoking for women, whereas nicotine is more important for men [37, 38]. This finding may explain why flavored LCC use is more prevalent among women and young adult cigar smokers [18, 19]. The FDA's Center for Tobacco Products has consequently listed research on cigar use, polyuse, and vulnerable populations among its top priorities for regulatory decision-making. What remains unclear is the potential of LCCs to facilitate or maintain addiction in the context of dual use, especially among vulnerable populations like women and young adults. The "addictive potential" of a drug is the likelihood that individuals will abuse or misuse the drug and experience undesirable consequences from use (e.g., adverse psychological effects, physical dependence) [39, 40]. The reinforcing efficacy of a drug is its ability to maintain or strengthen drug use behavior, and laboratory-based measures of reinforcing effects are good predictors of real-world addictive potential [41, 42]. Previous research on dependence in dual users has been inconsistent because it does not give sufficient attention to the addictive potential of LCCs compared with cigarettes (i.e., the relative reinforcing effects), regular dual users, or the impact of flavor [6, 14, 15, 23, 43-46].

Behavioral economic methods can address these gaps in the literature [47-49] and measure the reinforcing and relative reinforcing efficacy of LCCs [50, 51]. One behavioral economic tool, the purchase task, measures hypothetical consumption of a product at escalating prices to calculate demand [52]. From this task, several demand indices can be assessed, including: (a) *breakpoint* (the first price at which consumption is zero), (b) *intensity* (consumption at the lowest price), (c) *demand elasticity* (sensitivity of consumption to cost increases) and *cross-price elasticity* (sensitivity of consumption of

one product to cost increases of another product), (d) $\underline{O_{max}}$ (maximum expenditure for cigarettes), and (e) $\underline{P_{max}}$ (price at which expenditure is maximized) [49]. Products have greater addictive potential if their consumption is less sensitive to price (i.e., inelastic demand) [49]. The tool can also determine one product's substitutability for another product, that is, the change in the consumption of a product as the price of a second product increases (i.e., cross-price elasticity) [49]. The Cigarette Purchase Task (CPT) is a valid and reliable tool to measure cigarette demand, and its indices are associated with smoking behavior, dependence, and cessation [52-61]. However, its application to polyusers and to LCCs has been limited. Using an adapted version of the CPT, the proposed research will contribute to our knowledge of the addictive potential of LCCs compared with cigarettes among young adult regular dual users, and differences in those effects by flavor and sex. *This contribution will be significant because understanding the addictiveness of LCCs, how flavors influence their addictiveness, and if sex affects the addictiveness of LCCs and flavors will help public health practitioners develop cessation programs to better address tobacco addiction in high-risk populations, and policy-makers to regulate LCCs appropriately.* This research can markedly improve cessation rates in this high-priority group, and will inform regulatory and economic policy on cigars to discourage poly use. Increased cessation rates in young adults will significantly decrease their future morbidity and mortality.

B. **Innovation:** (1) The emphasis on the addiction potential of LCCs within a polyuse context represents a new approach to the study of tobacco use in young adults. By explicitly addressing the relative reinforcing values of LCCs and cigarettes, the conditions under which substitutability occurs for this population can be studied in detail. (2) Use of behavioral economic methods to evaluate the addiction potential of LCCs relative to cigarettes is a methodological innovation. Current survey–based studies cannot address the relative addictive value of these products, or take into account the influence of flavorings. Laboratory methods to address these issues have been costly, and have not been able to adequately address the substitutability of LCCs for cigarettes. The CPT has several advantages over other methods including being relatively easy for participants to understand and researchers to implement, and not requiring costly and specialized equipment [62]. Moreover, it can be more sensitive to detecting changes in the relative reinforcing effects of a product than subjective measures [63], making it uniquely suited to study the effects of flavors in LCCs. (3) Advances in CPT methodology to study flavors can be applied to the study of other characteristics like nicotine content, and will inform future research and policymaking. As a new investigator, the results of the proposed research will enable me to write a follow-up R01 to investigate flavored vs. unflavored LCC addictive potential and the association with subsequent smoking behaviors measured in real-time. In addition, I can submit future R level applications to further modify the CPT to study other polytobacco use and other tobacco product characteristics that may contribute to polyuse.

Hypotheses, Aims and Objectives:

- **Aims & Aim-Specific Hypotheses:**
  - Aim 1: To characterize the addictive potential of LCCs compared to cigarettes in dual users.
    - Hypothesis 1a: LCC demand elasticity will be higher and intensity lower than that of cigarettes, indicating less addictive potential of LCCs
    - Hypothesis 1b: The slope of the cross-price elasticity of LCCs and cigarettes will be positive and statistically significantly different from zero, indicating substitutability of LCCs as cigarette prices increase.

- Aim 2: To compare the addictive potential of preferred flavored vs. unflavored LCCs.
  - Hypothesis 2a: Flavored LCC demand elasticity will be lower and intensity higher than that of unflavored LCCs, indicating greater addictive potential fo flavored LCCs.
  - Hypothesis 2b: Cross-price elasticity of flavored LCCs and cigarettes will be positive and greater than the cross-price elasticity of unflavored LCCs and cigarettes, indicating greater substitutability of flavored LCCs.
- Aim 3: To explore sex-based differences in addictive potential of flavored and unflavored LCCs.
  - Hypothesis 3a: The addictive potential of flavored LCCs will be stronger in women than men, and the addictive potential of unflavored LCCs will be stronger in men than women, as measured by demand elasticity and intensity.
  - Hypothesis 3b: The substitutability of flavored LCCs will be greater among women than men and the reverse will be true for unflavored LCCs, as measured by cross-price elasticity.

See **Figure 1** for graphical representations of these hypotheses.

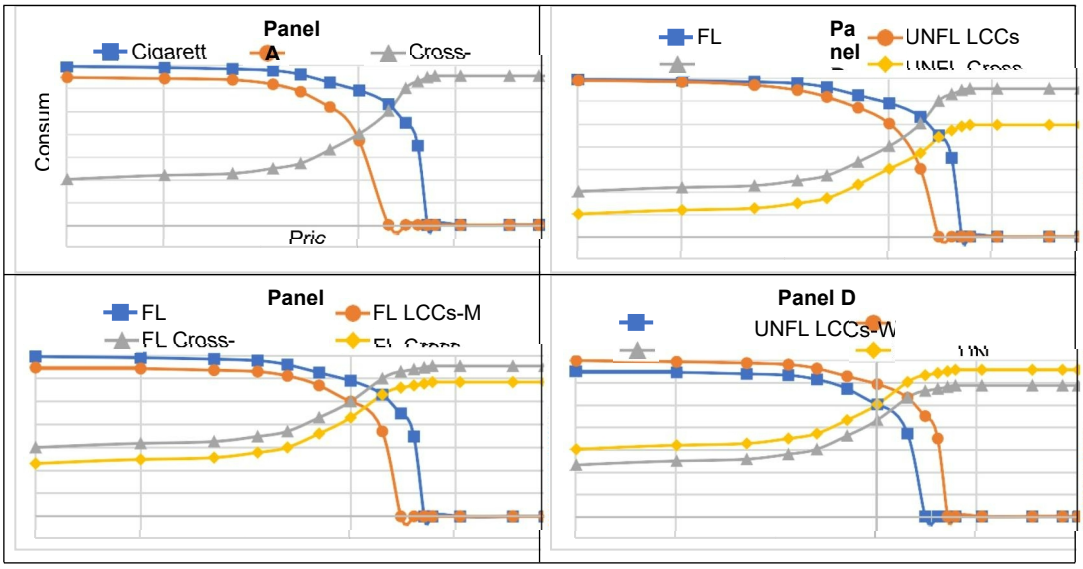

Figure 1. Hypothetical demand curves for cigarettes and LCCs (on a log-log scale). Panel A depicts the hypothesized self-reported demand for cigarettes and LCCs as the price for each product increases. It also depicts the hypothesized demand for LCCs as cigarette price increases (cross-price elasticity). Panel B depicts the hypothesized demand for flavored (FL) and unflavored (UNFL) LCCs, and the hypothesized cross-price elasticity of FL and UNFL LCCs for cigarettes. Panel C depicts the hypothesized demand and cross-price elasticity for FL LCCs among women (W) and men (M). Panel D depicts the hypothesized gender difference in demand and cross-price elasticity for UNFL LCCs.

Preliminary studies:

(1) Dual use of cigarettes and cigars in African American young adults: Dr. Mead conducted a mixed methods pilot study of the motivations and patterns of dual use of cigarettes and cigars in African American young adults (18-29) (unpublished). Using mobile phone-based ecological momentary assessments (EMA), 63 participants (retention rate: 82%) completed the 14-day study and completed EMA surveys as they smoked cigarettes and cigars in real-time. **Table 1** presents the descriptive statistics for the study sample. Over 14 days, participants smoked cigars an average of 9.5 days, and smoked an average of 4 cigars per day. Most (81%) of the participants smoked at least one cigar that was unaltered (i.e., without marijuana). Of those unaltered cigars, Black & Milds (a cigarillo brand) were the most popular brand (69%), and alcohol was the most popular flavor (75%). Alcohol flavoring was equally popular by sex (74% of men, 75% of women), but unflavored was more popular in men (70% vs. 54% of women) and fruit/dessert flavoring was slightly more popular in women (38% vs. 30% of men). **Results from this study indicated that: (1) cigars, specifically LCCs, were frequently smoked among young adult dual users, suggesting possible addictive potential, (2) flavored LCCs were highly popular, and (3) flavor preference might differ by sex. Moreover, the study indicated that the feasibility of sufficiently high retention rates and of recruiting an equal number of men and women.**

Table 1. Descriptive statistics of African
adult (18-29) dual users from 14-day pilc

Men
days smoked cigarettes
days smoked cigars
cigarettes/day (on days smoked)
cigars/day (on days smoked)
Cigar brands smoked[1] (n=51)
Black & Milds
Al Capones
Backwoods
Other
Smoked a flavored cigar[1] (n=51)
Cigar flavors smoked[1] (n=51)

(2) Sex and flavor effects on tobacco product use: Dr. Litt has extensive prior experience investigating the effects of sex and flavors on tobacco product use [64, 74]. In a pilot trial with 20 non-treatment-seeking smokers willing to try e-cigarettes and abstain from cigarette smoking for two weeks, participants were randomly assigned to use either an e-Juice flavored with tobacco and menthol or to an e-Juice flavored with tobacco only for 7-10 days, and the next 7-10 days were crossed over to the other condition [64]. Results indicated that, when women received an e-cigarette flavor that did not match their cigarette preference (menthol vs. non-menthol), they had lower nicotine concentrations and rated their e-cigarette as less likeable ($p<0.01$). Flavor had no effect on these outcomes in men. **These findings support the hypothesis that the addictive potential of flavored LCCs will be stronger in women than men. In addition, these studies show that Dr. Litt has the required expertise to provide mentorship in clinical research and addictions research.**

(3) Cigarette demand using the Cigarette Purchase Task (CPT): Dr. Tidey has published extensively on research using the CPT [57, 58, 60-62, 75]. In a study with 25 smokers with schizoaffective disorder (SS) and 24 control smokers (CS), SS and CS smokers were allowed to smoke ad lib through a smoking topography device and compared on indices of cigarette demand and delayed reward discounting (a behavioral economic index of impulsivity) [58]. The SS group exhibited a significantly higher intensity of demand than the CS group, but no differences were found for other indices. Ad libitum smoking was significantly positively correlated with intensity, O_{max}, and nicotine

dependence. **This study indicated the correlation between CPT indices of demand with smoking patterns and nicotine dependence. Moreover, it demonstrated the feasibility of CPT, and that Dr. Tidey has the required expertise to provide mentorship in behavioral economics research and CPT methodology.**

Study Design:

- **Study design:** The study will employ a prospective, randomized cross-over design with 125 non-treatment-seeking young adult (18-34) dual users of cigarettes and LCCs. Using the original CPT and the CPT modified for LCCs, we will assess demand for cigarettes as cigarette price increases, demand for flavored and unflavored LCCs as prices for these products increase, and demand for flavored and unflavored LCCs as *cigarette* price increases across two study visits. Prior to each visit, participants will receive (in random order) their preferred flavor and unflavored LCCs to use at home to validate their responses on the CPT. Study visits will take place 7 to 10 days apart. This strategy has been used in our previous study of e-cigarettes and shown to be a sufficient time period to examine the impact of flavors on likeability of the product [64]. See **Figure 2**.

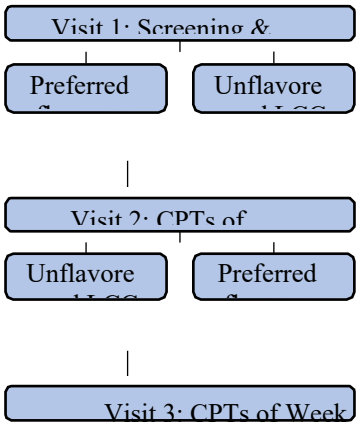

Figure 2. Randomized crossover study design

- **Sample size and justification:** We will enroll 125 non-treatment-seeking young adults (18-34) who are regular dual users of cigarettes and LCCs (see inclusion criteria for definition). Sample size calculation: No studies to date have investigated the main outcome for the proposed study: demand elasticity and intensity for flavored and unflavored LCCs, and cross-price elasticity of flavored and unflavored LCCs for cigarettes [65-68]. Published cross-price elasticities of LCCs for cigarettes range from 2.73 for little cigar sales [67] to 174.5 for cigarillo sales in exclusive, daily cigarette smokers [65]. Therefore, the sample size was calculated in G*Power 3 (94) using the standard medium effect size (d=0.5) for two independent means [69], in order to capture statistically significant differences by sex. With a sample size of 102, we can detect an effect size of 0.5 with 80% power and alpha=0.10. In Dr. Mead's pilot study with dual users [70], the attrition rate was 18%. Therefore, the final sample size of 125 participants will account for attrition.

- **Explain on what basis it is reasonable to assume that the sample size will be obtained**: Recruitment will take place over 18 months, requiring enrollment of about nine subjects per month. We will recruit from the community using flyers, subject referral, newspaper ads, radio ads, bus ads, and online sources like Craigslist.com. In Dr. Mead's pilot study with African American young adult dual users (18-29), 63 participants were recruited in four months (~16 participants enrolled per month) using primarily Craigslist and subject referral (unpublished). Therefore, the proposed recruitment timeline is feasible.

- **Method(s) of data analysis:** Descriptive statistics including means (SDs) and frequencies (percentages) will be reported to describe demographic characteristics and smoking history.

From the CPTs, demand curves for LCCs (own brand, preferred flavor, and unflavored) and cigarettes will be graphically plotted, and consumption as a function of cost will be calculated using the Exponential Model of Demand [71, 72]. From the demand curves, the following indices will be calculated using standard equations [55, 72]: (a) breakpoint, (b) intensity, (c) elasticity and cross-price elasticity, (d) O_{max}, and (e) P_{max}. For Aims 1 and 2, the demand indices for own brand of LCCs, preferred flavor LCCs, unflavored LCCs, and cigarettes will be compared. In addition, the cross-price elasticity will be calculated using an extension of the exponential model of demand to determine how demand for LCCs (own brand, preferred flavor, and unflavored) changes as a function of cigarette price [73], adjusting for age, gender, race, and menthol status. Survey-based measures of LCC impressions, risk perceptions, and dependence will be calculated, compared by product using Analysis of Variance (ANOVA) tests, and correlations with demand indices will be examined. For Aim 3, the models will be stratified by gender to compare demand indices in women and men. In post-hoc analysis the demand indices will be stratified by race/ethnicity to detect any differences in the addictive potential of the products.

Subject Characteristics:

- Age: 18-34 years
- Ethnicity: All are eligible
- Gender: approximately 50% women and 50% men
- Vulnerable Populations: No special vulnerable populations (such as fetuses, neonates, pregnant women, children, prisoners, and institutionalized individuals) will be involved.
- Other characteristics: None
- Inclusion Criteria:
  - Current regular dual user of little cigars/cigarillos (LCCs) and cigarettes, defined as: (a) report smoking cigarettes on ≥ 8 of the past 30 days, and (b) report smoking unaltered LCCs (without marijuana) on ≥ 8 of the past 30 days.
  - Able to speak, read and understand English
  - Age 18-34 years of age
  - Stable residence (not planning to move during study period)
  - Not intending to quit smoking cigarettes or LCCs within the next 2 weeks
  - Urinary cotinine level ≥100 ng/mL (one re-test allowed)
- Exclusion criteria:
  - Pregnant for women (verified by urine pregnancy test at Visits 1 and 2)
  - Current use of (or plans to use in the next 2-3 weeks) nicotine replacement products or cessation products (e.g., bupropion) to minimize confounding effects of another product)
  - Positive saliva alcohol level (SAL) screen (>= 10 mg/dL; one re-test allowed; assessed at Visits 1, 2, and 3)

- Illicit drug use other than marijuana (verified by positive drug toxicology test at Visits 1 and 2; one re-test allowed)
- Met criteria for Cannabis Dependence assessed by the Cannabis Use Disorders Identification Test-Revised (CUDIT-R)

Study Procedures:

- **Screening Procedures, who will perform them, where**: There are two stages for screening. First, individuals who are interested in the study will be directed to our online survey. The brief, online screening survey will provide further information about the study and assess individuals' initial eligibility by asking about the following: sex, age, ability to read and write in English, cigarette smoking, LCC smoking, plans to quit smoking, current use of or plans to use nicotine replacement or cessation products, pregnancy status (if female), plans to move in the next 2-3 weeks, and willingness to come to UCHC, UConn Storrs, or UConn Hartford for study visits. The screening survey will also ask where they heard about the study. If they are eligible based on the online screening survey, the screening survey will collect their contact information. This initial screener will take about 5 minutes. Individuals who do not want to complete the screener online will be given the option to call our research staff to complete it over the phone. Second, research staff will contact (via phone and/or email) the individuals who initially screened as eligible and administer the CUDIT-R over the phone to assess marijuana dependence. If they are still eligible, research staff will administer the COVID-19 screener to ensure that the participant does not have COVID-19 exposure/symptoms. If no symptoms are present, the research staff will invite them to come to the study site for an in-person screening visit (Visit 1), and ask for their date of birth in order to book the appointment in Epic.

  The screening visit (Visit 1) will take place at the UCHC CRC, UConn Storrs, or UConn Hartford. At Visit 1, research staff will meet the participant outside of the main entrance to perform the exhaled breath CO test in order to minimize risk of the spread of COVID-19. Once it is recorded, staff and participant will proceed inside to complete the rest of the study procedures. Staff will administer a saliva alcohol level (SAL) test to ensure the person's capacity to complete study procedures. One re-test will be allowed at that same visit. If the person does not pass the SAL re-test, we will ask them if they would like to reschedule Visit 1. If they reschedule Visit 1, we will instruct them to refrain from alcohol use prior to the visit. If they fail the SAL test at the second visit, they will not be eligible to continue. Those who pass the SAL test will be given more information about the study and provided with the written consent form. After consent, research staff will assess inclusion/exclusion criteria. They will verify the inclusion/exclusion criteria already assessed in the initial screener. In addition, they will administer urine pregnancy (for women only), drug toxicology, and cotinine tests, and the cotinine supplemental survey. The UCP 5-panel urine drug toxicology test kits will test for THC (marijuana), cocaine, opiates, amphetamines, and benzodiazepines. A positive screen for THC will not make individuals ineligible, but a positive screen for other substances will make the individual ineligible. The urinary NicQuick LFIA test kit will test for cotinine levels. Participants who do not pass the drug or cotinine tests will be allowed one re-test. In this situation, the study team will ask the participant if they would like to reschedule Visit 1 to be re-tested for the urine test that they failed. If the participant agrees, at the next visit the study team will conduct the relevant re-test. If the participant

still does not pass it, they will not be eligible to continue. If they do pass it, the screening procedures will resume. We will record all new test results on new case report forms.

Screening results will be recorded and placed in the data collection records. Individuals who are still eligible after completing all screening procedures will proceed with the study procedures. All screening procedures will be performed by the PI (Dr. Mead), trained UCHC Clinical Research Center (CRC) research assistants, or trained UConn undergraduate student research assistants, and s/he will record eligibility using the attached "Inclusion/Exclusion Criteria Screen."

- **Study Procedures, who will perform them, where:** See **Figure 2** for overview. All procedures will be conducted at the UConn Health campus in Farmington, the UConn campus in Storrs, or the UConn campus in Hartford; which location depends on the participant's preference. At Visit 1 after the screening procedures have been completed, participants will complete the following:

    - **Vitals form:** to record blood pressure, pulse, height (V1 only), and weight. If the equipment is not available, we will rely on self-reports for height and weight, and not record BP or pulse.

    - **Demographics survey:** to capture demographic (age in years, sex, marital status, ethnicity, race, number of household members) and socioeconomic (education, current enrollment in school, employment status, receipt of public assistance, total household income, financial status) factors.

    - **Tobacco Use History and Perceptions Questionnaire:** developed by the PI (Dr. Mead) in her pilot study of African American young adult dual users (unpublished). The questionnaire asks about their history of smoking cigarettes, LCCs (without marijuana), and LCCs (altered to contain marijuana, also called 'blunts'). It also asks about their history of using other tobacco products, beliefs about the harmfulness, social acceptability, and addictiveness of plain (unflavored) and flavored LCCs compared to cigarettes, and their confidence in their ability to quit smoking cigarettes, plain LCCs, and flavored LCCs (i.e., self-efficacy).

    - **30-Day TimeLine FollowBack (TLFB):** to estimate the number of cigarettes, LCCs, marijuana products, and other tobacco products used for the past 30 days [74].

    - **Fagerström Test for Cigarette Dependence (FTCD):** to assess the intensity of physical addiction to cigarettes using six items that measure consumption, the compulsion to use, and dependence [75, 76]. It has been adapted to additionally ask about LCC consumption, compulsion, and dependence.

    - **Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R)** (previously called the Minnesota Nicotine Withdrawal Scale): to measure the withdrawal effects of smoking cessation as an assessment of nicotine dependence [77].

    - **Questionnaire of Smoking Urges (QSU)-Brief:** to comprehensively assess craving using 10 items that measure their thoughts and feelings about cigarette craving [78, 79]. It has been adapted to additionally ask about LCC craving.

- **Respiratory Form and Adverse Events log**: Subjects will rate potential adverse effects (cough, throat irritation, rhinitis, and mouth irritation, which have been noted in studies of cigarette smokers. We will assess symptoms on a 4-point scale: 0=absent, 1=mild, 2=moderate and 3=severe. Other AEs will also be recorded and severity rated.

- **Cigarette Evaluation Scale (CES):** to assess the subjective rewarding and aversive effects of cigarette smoking [80]. It has been adapted to additionally ask about LCC smoking.

- **Liking Survey:** to assess participants' likes and dislikes for foods, physical activity, common experiences, and tobacco products using a gLMS scale.

- **Cigarette Purchase Task (CPT):** to collect hypothetical consumption of cigarettes at escalating prices to calculate the demand breakpoint, intensity, elasticity and cross-price elasticity, O_{max}, and P_{max} [52, 55]. This is a measure of addictive potential of a product.

- **Cigar Purchase Task:** adapted from the CPT to ask about consumption of LCCs.

- **Cross-Price Purchase Task:** to collect hypothetical consumption of LCCs at increasing cigarette [49]. This will help to determine the substitutability of LCCs for cigarettes when cigarettes are prohibitively expensive.

Next, participants will be shown one brand of LCC in several flavors (i.e., fruit, dessert, and alcohol)—as well as plain tobacco (unflavored)—and allowed to handle and smell them. They will then be asked to choose their preferred flavor. It is assumed that participants will have little difficulty selecting their preferred flavor, given that they are regular dual users and will likely have smoked a variety of flavors in their lifetime. Participants who prefer the unflavored LCC will be asked for their second preferred flavor. Next, they will be randomized to receive either their preferred flavor or unflavored LCC using urn randomization to balance groups on menthol cigarette status and sex. Based on their baseline smoking rate calculated from the TLFB, the study staff will dispense a 1-week supply of LCCs. The study staff will ask the participants to smoke the study LCCs in place of their normal LCCs as much as they are able to, and to smoke the study LCCs unaltered (without marijuana). At the end of the visit, research staff will provide participants with their personal (single-user) iCO Smokerlyzer device and instruct them on how and when to use it.

One to two days before Visit 2, research staff will use Webex to do a video call with participants. The time will be pre-arranged at Visit 1 with reminders via phone, email, or text. Participants will need to use their webcam on their phone or computer for the call. During the video call, research staff will observe as participants use their iCO device to measure their CO level and email the results to the staff. Staff will confirm receipt of the email prior to ending the call. The video call will ensure that participants are using the device correctly and giving correct readings. Alternatively, the participants can choose to video record themselves using the iCO and emailing the results to the staff.

Approximately 7-10 days after Visit 1, participants will return for Visit 2. The day prior to the visit, staff will email the Qualtrics surveys to participants so that participants can do them online ahead of time if they want to. Study staff will initially meet participants outside to administer the

CO test, then proceed inside for the rest of the study visit. Participants will return unused Week 1 products that were provided by the study, and complete the following procedures:

- **SAL test:** to ensure capacity to complete study procedures (one re-test allowed)
- **Urine drug toxicology test**: will be dropped from study if they test positive for illicit drugs (excluding marijuana). Participants who test positive will be asked if they would like to be re-tested. If they agree, their visit will be scheduled within the next 3-7 days. If they still test positive, they will be dropped. If they do not test positive, the study team will conduct the rest of Visit 2 procedures.
- **Urine pregnancy test for women:** will be dropped from study if they test positive
- **TLFB:** to measure cigarette, LCC, marijuana, and other tobacco product use since the last visit
- **Past 7 Day Smoking:** use of cigarettes, study assigned LCCs, and other brand of LCCs in past 7 days, and reasons for use of other brand
- **MTWS-R**
- **QSU-Brief**
- **Respiratory Form and other Adverse Effects log**: since the last visit
- **CES:** adapted to ask about the study-provided Week 1 LCCs
- **Tobacco Perceptions Questionnaire:** beliefs about the harmfulness, acceptability, and addictiveness of Week 1 LCCs, as well as self-efficacy to quit Week 1 LCCs (questions are adapted from those asked about own brand in Visit 1 Tobacco Use History Questionnaires).
- **CPT**
- **Cigar Purchase Task:** adapted to assess Week 1 LCCs
- **Cross-Price Purchase Task**: adapted to assess Week 1 LCCs within the context of cigarette prices.

Next, participants will crossover to receive the other LCC type for one week following the same procedures. The amount they are given will be based on their baseline smoking from the TLFB.

One to two days before Visit 3, research staff will again use Webex for a pre-arranged video call to observe participants using the iCO device, or arrange for the participant to email a video that shows them using the iCO device and emailing results to study staff. The same procedures will be followed as in the first video call.

About 7-10 days after Visit 2, participants will return for Visit 3. The day prior to the visit, staff will email the Qualtrics surveys to participants so that participants can do them online ahead of time if they want to. Staff will first administer the CO test outside before proceeding inside to complete the study visit. Urine drug toxicology and SAL tests will be performed. If participants fail one or more of these tests, we will allow one re-screen per the earlier descriptions. The same questionnaires as Visit 2 will be administered, except they will ask about Week 2 instead of Week 1 LCCs provided by the study. If at Visit 3 a participant reports an AE that is ongoing and probably related to the study, the study team will call the person about 7 days after the visit to ask if the AE is resolved. If it did not resolve, the study team will advise the person to see their doctor and reduce their smoking. The study team will note the call on the AE log.

Participants will be financially compensated $75 at the end of visit 1, $75 at the end of visit 2, and $100 at the end of visit 3 (up to $250 total per person). The extra $25 at visit 3 is a bonus payment for completing all study procedures. Participants seen at UConn Health in Farmington or UConn in Hartford can choose to either receive checks payable to cash or e-gift cards to Walmart or Dominos (their choice). Participants seen at UConn in Storrs can choose to either be emailed e-gift cards or mailed checks payable to cash via certified mail. Participants can keep their iCO device.

If the research staff are unable to get a participant to come in to the study site for Visit 3 within the 10-day window or if the participant feels more comfortable doing the visit remotely, they will administer the survey instruments with participants over the phone. To receive the payment, Visit 3 phone participants can choose one of three options for receiving payment: (1) mailed a check via certified mail through UConn Health; (2) pick up a check and sign the receipt at the CRC at UConn Health; or (3) emailed an e-gift card. For the certified mailed checks, CRC staff will receive written notification that the person signed for the check, and this documentation will be kept with the other check receipts. A record of the emailed e-gift card will be kept in the participant's file and in a tracking log on the CRC secure drive.

Participants will also be informed that they can refer up to three friends for additional compensation. They will receive $10 per friend referred who is randomized (max: 3 friends). The friend must be enrolled, eligible, and complete Visit 1 study procedures (i.e., randomized to either flavored or unflavored LCC) for the participant to receive the additional compensation.

All study procedures will be completed by the PI (Dr. Mead) or a research assistant. They will keep track of the procedures at each visit using the attached "Visit Checklist."

At the end of Visit 3, research staff will inform participants that they do not endorse smoking and recommend cessation. They will ask if they would like smoking cessation information, and provide accordingly.

Addendum: Participants who fail urine test but pass CO test

For participants who, at Visit 1, fail the urinary cotinine test but have an exhaled breath CO of ≥4 ppm, we will freeze their urine sample for future testing to determine the reason for the discrepancy.

For participant #16, who failed the urinary cotinine test but passed the CO test at Visit 1, we will re-test his urine at follow-up visits using the cotinine test strips. We will also freeze his urine samples for future testing to determine the reason for the discrepancy.

Addendum: Participants who fail cigarettes/cigar inclusion criteria during screening due to past 30-day jail time

Participant #029 did not meet the inclusion criteria of # of cigarettes and cigarillos smoked in the past 30 days because, until recently, he was in jail. We would like to re-contact him 30 days after his initial screening for recruitment and enrollment. We would like to follow similar procedures for others who were released from jail within the past 30 days at the time of screening.

- **Describe length of subject's participation in the study including number of visits, frequency of visits, and length of visits:** Participants will be in the study for 2-3 weeks. They will come to 3 study visits, about 7-10 days apart. Visit 1 will take about two hours, and Visits 2-3 will take about an hour each.

Recruitment:

- **All Recruitment Methods and Materials:** Participants will be recruited from the community using flyers, subject referral, newspaper ads, bus ads, radio ads, and online sources. Flyers (see attached) will be distributed at colleges, community centers, bars, and music venues in the communities in and near Farmington, Hartford, and Storrs. We will also run ads in the local buses and on local radio stations (see attached). Each radio ad runs for about 2 weeks, and each bus ad for about 4 weeks. We will also run ads in local newspapers, like the Yankee Flyer (see attached). Online sources, such as Facebook, Craigslist, and Google Ads, will also be used (see attached), and work especially well for recruiting young adults [81, 82]. We will also use these online ads for the UCHC Broadcast email. Lastly, we will ask participants to refer their friends to the study, and give them cards to distribute (see attached). All recruitment materials contain the study's phone number, website address to complete the screener, Google voice number to text, and email address. For participants who call, research staff will complete the screener over the phone. In addition to phone, interested individuals may also contact the study staff in response to recruitment materials by email or text. Study staff will contact individuals by phone, voice, and/or text to determine interest in participating in the study and, if interested, to refer them to the online screener or set up a phone call for screening. Recruitment will take place over 13 months, requiring enrollment of about 10 subjects per month. In Dr. Mead's pilot study with young adult dual users, 63 participants were recruited in four months (~16 participants per month) using primarily Craigslist and subject referral. Therefore, the recruitment timeline is feasible. All recruitment procedures will be conducted by the PI (Dr. Mead), trained CRC research assistants, or trained UConn undergraduate student research assistants. Google voice will be used for texting only, and used from a secure device. It has been approved by IT security. A uchc email address has been obtained for the study, and will only be used from a secure device.

- Participants may receive reminder phone calls, text messages, and/or emails about upcoming appointments.
- ResearchMatch.com: Potential volunteers will be contacted by ResearchMatch with IRB-approved recruitment content for this study, not including direct study contact information such as study phone number. Volunteers will then have the option of replying 'yes' or 'no' through a set of quick links available in the recruitment message. If a volunteer chooses to respond in the affirmative, they will authorize ResearchMatch to release their contact information to the PI (or ResearchMatch designee) who will be responsible for managing that information according to institutional guidelines.

Consent Process:

- Process for Obtaining Consent (timing, location, length of discussion, time for consideration): Written informed consent will take place at Visit 1 at the CRC at UConn Health, at Dr. Duffy's lab at UConn Storrs, or in a private conference room at UConn Hartford. It will take place after a SAL analysis has verified the individual's capacity to complete study procedures. One re-test will be allowed. Study staff (Dr. Mead, trained CRC research assistants, or trained UConn undergraduate student research assistants) will explain the study and administer consent. All participants will sign an IRB approved informed consent form. The form will explain what each participant can expect during the course of the study, potential risks and benefits, freedom to withdraw from the study at any time, and the procedure for pursuing a complaint against the institution. Study candidates will be advised that they will be free not to participate in this protocol, and if they elect to participate may withdraw at any time. Participants will be given all the time they want to ask questions about the study and decide whether or not they want to participate. The participants will also indicate on the consent form whether or not they want to be contacted for future research studies. After the participant gives informed consent, basic inclusion/exclusion criteria will be assessed. We expect the entire Visit 1, including consent, to take about two hours. It will take place in a private office.

- Who will Provide Consent (e.g. subject, legally authorized representative): The participant will provide written informed consent.

- Assessment of Capacity: Only participants who are able to provide consent will be enrolled. We will conduct SAL analysis to ensure study candidate is not incapacitated by alcohol.

- Requests for Waivers Consent: N/A

Budget / resources: Funding is being provided by the Patterson Trust Mentored Research Award for 2 years. $95,000 total ($50,000 in Year 1, and $45,000 in Year 2). See attached funding agreement for the full budget.

Dissemination: Results will be disseminated via presentations at conferences sponsored by professional societies, such as the Society for Research on Nicotine and Tobacco (SRNT) Annual Meeting, as well as articles published in peer-reviewed journals.

Additional Information:

PROTECTION OF HUMAN SUBJECTS

A. Risks to Human Subjects

A1. Human Subjects Involvement, Characteristics, and Design. To achieve the three specific aims for the proposed research, human subjects will be recruited to complete survey instruments. The study does not involve any investigational new drugs or devices. The enrollment ceiling is 125 participants (approximately 50% women and 50% men) age 18-34 years of all ethnic and racial groups. At three study visits, participants will complete a series of surveys for data collection purposes. Urine pregnancy (for women), urine drug toxicology, and saliva alcohol level (SAL) screen tests will be conducted at Visit 1 to determine initial eligibility for the study. Urine pregnancy and drug toxicology tests will also be conducted at Visit 2 to determine continued eligibility, and SAL test will also be conducted at Visits 2 and 3 to ensure capacity to complete study procedures.

Inclusion Criteria (assessed at Visit 1):

1. Current regular dual user of little cigars/cigarillos (LCCs) and cigarettes, defined as: (a) report smoking cigarettes on ≥ 8 of the past 30 days, and (b) report smoking unaltered LCCs (without marijuana) on ≥ 8 of the past 30 days.
2. Able to speak, read and understand English
3. Age 18-34 years of age
4. Stable residence (not planning to move during study period)
5. Not intending to quit smoking cigarettes or LCCs within the next 2 weeks
6. Urinary cotinine level ≥100 ng/mL (one re-test will be allowed)

Exclusion Criteria (assessed at Visit 1 unless otherwise noted):

1. Pregnant for women (verified by urine pregnancy test at Visits 1 and 2)
2. Current use of nicotine replacement products or cessation products (e.g., bupropion) or intend to use within the next 2 weeks to minimize confounding effects of another product)
3. Positive alcohol screen (saliva alcohol level (SAL) >= 10 mg/dL; one re-test allowed; assessed at Visits 1, 2, and 3)
4. Illicit drug use other than marijuana (verified by positive drug toxicology test at Visits 1 and 2; one re-test allowed)
5. Met criteria for Cannabis Dependence assessed by the Cannabis Use Disorders Identification Test-Revised (CUDIT-R) (assessed during phone screening)

Participants from all racial/ethnic groups are eligible for this study if they meet the inclusion/exclusion criteria. The study sample will be drawn from this source population of young adults (18-34) because dual use of cigarettes and LCCs is most prevalent in this group. Efforts will be made to extend accrual to a representative population through community-based recruitment sampling. Recruitment strategies include local media advertisements (newspaper, bus, radio), flyers, subject referral, and online sources (Craigslist.com). To enhance retention, participants will be contacted up to 5 times to make the appointment for the study visit; if they are not responsive after 5 contacts, they will not be contacted anymore. Contacts will be made via email, phone, and/or text messaging, depending on participants' preferences. Participants will be approximately 50% women and 50% men in order to meet Specific Aim 3. Because this is a crossover trial, all participants will receive the same intervention. No

special vulnerable populations (such as fetuses, neonates, pregnant women, children, prisoners, and institutionalized individuals) will be involved.

A2. Sources of Materials. Research data will be obtained through questionnaires collected in-person via electronic or paper-based versions for the questionnaires. SAL, drug toxicology, and urine pregnancy tests will be collected solely for determination of eligibility and continued participation in the proposed study. Information on the specific instruments is provided in the Research Strategy section.

A3. Potential Risks. The potential risks from the study procedures include: (1) the risk of unauthorized disclosure of confidential material; (2) the burden of time to complete the research procedures; (3) exposure to potentially stressful circumstances; and (4) the risks of smoking. These issues are considered in the following paragraphs.

1) Risks of unauthorized disclosure of confidential material: Information about demographics, smoking history, current tobacco use, and risk perceptions will be collected about each participant. Data will be collected via paper forms and electronically, and stored electronically. There may be a small risk of unauthorized persons illegally accessing the data, but procedures will be in place to minimize this risk, including electronic data encryption and password protection, use of Qualtrics or REDCap for data management and storage (a secure cloud-based system), unique identifying codes and de-identification of the data, storage of hard copies of data in locked cabinets.

2) Burden of time to complete the research procedures: The procedures involved with data collection in this study require a moderate amount of time and multiple study visits.

3) Exposure to potentially stressful circumstances: Efforts to switch away from one's usual LCCs may be considered stressful by some participants.

4) Risks of smoking and toxicant exposure: Smoking is a significant risk factor for heart disease, cancer, respiratory disease, and many other health problems, and dual use may enhance those risks. Although we will choose a popular brand for the study-provided LCCs, they may not be the usual brand smoked by some participants. Because they vary in size and content, LCC brands vary in their levels of nicotine and toxicants. Therefore, the study-provided LCCs may increase some participants' nicotine and toxicant exposure compared to their usual brand.

B. Adequacy of Protection Against Risks

B1. Recruitment and Informed Consent. Community-based recruitment will take place using local media advertisements (newspaper, bus, radio), flyers, subject referral, and online sources (Craigslist.com). Participants will initially be screened over the phone. Those who are initially eligible will be scheduled for an in-person screening appointment (Visit 1). At Visit 1, potential participants will first provide a SAL to ensure they are able to take part in further procedures. If SAL >= 10 mg/dL, one re-test will be allowed. If the individual still fails the SAL test, s/he will be deemed ineligible. If the SAL test is passed, potential participants will be given a thorough description of the study and asked to provide written informed consent. Next, basic inclusion/exclusion criteria will be assessed. Trained research staff or Dr. Mead will complete the consent procedures.

B2. Protections Against Risks.

1) Risks of unauthorized disclosure of confidential material: All research data will be coded to prevent identification of subjects. We will use a 5 digit study code (CRC study #) followed by a 3 digit number that reflects how many people enrolled in the study. The master list relating subject code numbers to their names will be kept separately in a locked file cabinet. Data generated during the course of this study will be de-identified (all identifiers removed and labeled within unique subject code). Paper copies of the data will be stored in a locked file cabinet. Electronic data will be encrypted, password protected, and kept on the secure Qualtrics or REDCap cloud-based data management software. Only the PI and research staff will have access to the master list.

2) Burden of time to complete the research procedures: Subjects will be compensated for the time spent participating in research assessments for this study. Every effort will be made to streamline the study visits. Study visits will be scheduled at the subject's convenience. Subjects will be free to refuse to complete any assessments at any time, and they may withdraw at any time.

3) Exposure to potentially stressful circumstances: We do not anticipate this issue will be significant because dual users often use more than one brand of LCC. However, subjects may withdraw at anytime if they feel stressed from study participation.

4) Risks of smoking and toxicant exposure: To minimize this risk, only regular dual users of both cigarettes and LCCs (defined above) who are not interested in quitting will be eligible to participate, and participants may withdraw or stop study-provided LCC use at any time. When study-provided LCCs are dispensed by study staff at Visits 1 and 2, participants will also be given a sheet of paper with all seven of the warning labels that, starting on August 13, 2018, will be required to be on cigar packages by the FDA. At the end of Visit 3, we will advise participants that we do not endorse smoking and recommend cessation. We will ask if they would like cessation materials, and will provide materials asrequested.

C. Potential Benefits of the Proposed Research to Human Subjects and Others

The risks entailed in this study are considered reasonable and minimal because the source population (from which the study sample will draw) are individuals who are currently using both cigarettes and LCCs and have no interest in quitting. There will be an additional burden of time to complete the research procedures, but we will take every effort to streamline the assessments. There are no direct benefits to subjects for participation. We believe that the small risks of the study are outweighed by the potential benefits of understanding the addictive potential of LCCs and how that addiction changes when flavor is eliminated. We expect that there will be societal benefits in understanding the addictive potential of flavored vs. unflavored LCCs in young adult dual users, which will be useful for cessation programs and regulatory purposes.

D. Importance of Knowledge to be Gained

Smoking is one of the leading health problems in the U.S. The burden of multiple tobacco product and LCC use is growing, particularly in young adults. Our understanding of the addictive potential of LCCs, and the moderating effects of flavor and sex, is limited at this time. By providing information about their addictive potential, we expect to inform cessation efforts targeting young adult dual users and regulatory decision-making on LCCs for prevention and cessation.

DATA AND SAFETY MONITORING PLAN

Dr. Mead will assume primary responsibility for safety of this study, executing the data and safety monitoring plan (DSMP), and complying with reporting requirements, under the mentorship of Drs. Mark Litt, and Jennifer Tidey. Because the study is low-risk and single-site, there will not be a Data and Safety Monitoring Board. Dr. Mead will meet with the study personnel on a weekly basis, and will be available at any time to identify and solve problems in the study's implementation, and provide advice on any adverse events experienced by participants during the study. The research assistant will be responsible for the monitoring of participants and will report to Dr. Mead as needed.

A. Safety Monitoring

The proposed study poses low risk of harm to participants; therefore, we expect that SAEs will be rare and not related to study participation. We will collect all respiratory and other AEs on log forms (see attached) and in a tracking database. Each AE will be graded (mild, moderate or severe). SAEs will be also noted. Additionally, we will note probable cause (unrelated, possibly related, or definitely related to the study). AEs and SAEs, even those clearly unrelated to the study such as accident or illness, will also be reported to Dr. Mead and either Drs. Jon Covault, or Mario Perez (who are MDs). Any concerning events that could be related will be reviewed on an ongoing basis at study meetings. Dr. Mead and either Drs. Covault, or Perez will determine how to proceed in consultation with Drs. Mark Litt and Jennifer Tidey as needed.

Participants who experience any of the following will be said to have experienced an SAE, as defined by the FDA:

- Death
- Suicide or homicide attempt
- Persistent, serious suicidal or homicidal ideation, with intent and plan
- Congenital Abnormality or permanent disability
- Life-threatening events
- Overnight hospitalization (excluding planned surgeries or other planned procedures)

Any participant who experiences an AE or SAE will be assessed for causality, and referred to treatment if necessary. Any participant who experiences an SAE will be advised regarding options to continue or terminate participation in the study. All AEs will be reported to the IRB on an annual basis. All SAEs will be reported to the IRB of record within the required time limits.

B. Data Monitoring

Dr. Mead will assume primary responsibility for data accuracy and protocol compliance. Data will be collected securely electronically and double-checked by research staff. Audits of randomly selected participant files will be conducted quarterly to check on accuracy of data entry and protocol adherence. Adherence to protocols will also be ensured by ongoing supervision by Dr. Mead, who will report regularly to Drs Litt, and Tidey in their regularly scheduled mentorship meetings.
Protocol deviations as a result of staff error will be reported to the IRB with a protocol deviation report form. The protocol deviation report will outline the root cause of the problem and establish a plan of

action to avoid similar errors in the future. Minor protocol deviations not within the control of the study team will be reported annually to the IRB as per the regulatory guidelines.

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APPENDIX A
INVESTIGATOR INITIATED PROTOCOL TEMPLATE

Additional Details Pertaining to Study Design for Clinical Trials

1. For a clinical trial (e.g. a Phase I, II or III study), the use of the intervention must be fully described e.g., the treatment regimen for use of drugs, placebo, medical device etc. Also include plans for receipt of test article, storage, dispensing and reconciliation.

   Participants will be given a one-week supply of preferred flavor little cigars/cigarillos (LCCs) and a one-week supply of plain (unflavored) LCCs (order randomized). We will dispense a brand of LCCs that are already on the market and popular, such as Black and Milds. Every participant will be given the same brand and presented with the same flavor choices. The products that we will dispense are not new nor experimental. Moreover, it should be noted that the participants will be regular smokers of LCCs in order to qualify for the study.

   We will order our supply of LCCs from an online vendor and store them in a secured location in the CRC. Only trained study personnel—the PI (Dr. Mead), CRC research assistants, or UConn undergraduate student research assistants—will dispense the products at Visits 2 and 3. Study personnel will use the participants' normal usage patterns of LCCs to determine how many to dispense. At the end of each one-week period, participants will return unused LCCs to the study personnel. Unopened products can be used for future participants.

2. Provide a description of known adverse events due to the intervention and the plan to deal with such adverse events (e.g. does reduction, removal of device, removal from trial.):

   Participation in the study should not pose additional risks to participants. To be eligible to participate in the study, participants must already be a current, regular dual user of LCCs. That is, they are already exposing themselves to the harms associated with LCC use. Therefore, the proposed study poses low risk of harm to participants, and we expect that SAEs will be rare and not related to study participation.

   We will collect all respiratory and other AEs on a log (see attached) and enter them into a tracking database. Each AE will be graded (mild, moderate or severe). SAEs will be also noted. Additionally, we will note probable cause (unrelated, possibly related, or definitely related to the study). AEs and SAEs, even those clearly unrelated to the study such as accident or illness, will also be reported to Dr. Mead, and to either Dr. Covault or Dr. Perez. Any concerning events that could be related will be reviewed on an ongoing basis at study meetings. Drs. Mead and Covault or Perez will determine how to proceed in consultation with Drs. Litt and Tidey as needed.

   Participants who experience any of the following will be said to have experienced an SAE, as defined by the FDA:
   • Death
   • Suicide or homicide attempt
   • Persistent, serious suicidal or homicidal ideation, with intent and plan

• Congenital Abnormality or permanent disability
• Life-threatening events
• Overnight hospitalization (excluding planned surgeries or other planned procedures)

Any participant who experiences an AE or SAE will be assessed for causality, and referred to treatment if necessary. Any participant who experiences an SAE will be advised regarding options to continue or terminate participation in the study. All AEs will be reported to the IRB on an annual basis. All SAEs will be reported to the IRB within the required time limits.

3. Describe circumstances that may lead to a subject being removed from the trial by the PI, e.g. due to failure to follow study procedures, and the process for doing so:

Participants who fail to show up to their appointments five times in a row will be removed from the study. Study staff will notify them via email or phone.

4. Describe any stopping rules for the study*:* **In the event that several SAEs are recorded in a short space of time (i.e., more than 6 in one month), or if a pattern of SAEs becomes apparent (e.g., one treatment condition results in many more SAEs than the other condition), Dr. Mead and her mentors on the study Drs. Jonathan Covault, Mario Perez, Mark Litt, and Jennifer Tidey review the data and make one of the following determinations: 1) continue recruitment unchanged; 2) continue after a protocol amendment; or 3) stop recruiting pending further investigation.**

5. Additional Comments by PI*:* **None**