STUDY PROTOCOL:

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2016-1)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Electronic Cigarette Use in Young Adult Men and Women			
Principal Investigator: Deepa Camenga		**Yale Academic Appointment:** **Assistant Professor**	
Department: Emergency Medicine			
Campus Address: 464 Congress Avenue Suite 260, New Haven CT 06519			
Campus Phone : 2037378310	**Fax :** 2037854580	**Pager:** 2034944078	**E-mail:** deepa.camenga@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone :	**Fax :**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone :	**Fax :**	**E-mail:**	
Business Manager: Breonna Harrington			
Campus Phone : (203) 737-4210	**Fax :** 2037854580	**E-mail:** breonna.harrington@yale.edu	

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

❑ **xxxxxxNo**

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an

invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

❑ **xxxxNo**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale University PET Center
☒ YCCI/Church Street Research Unit (CSRU)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ YCCI/Hospital Research Unit (HRU)
☐ Yale Cancer Center/Smilow
☐ YCCI/Keck Laboratories
☒ Yale-New Haven Hospital
☐ Yale-New Haven Hospital—Saint Raphael Campus
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:

b. External Location[s]:

☒ APT Foundation, Inc.
☐ Haskins Laboratories
☐ Connecticut Mental Health Center
☐ John B. Pierce Laboratory, Inc.
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Veterans Affairs Hospital, West Haven
☐ Other Locations, Specify:
☐ International Research Site
(Specify location(s)): SATU 1 Long Wharf New Haven, CT

c. Additional Required Documents *(check all that apply)*:

☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Yale University RSC (YU-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ *Nursing Research Committee	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

STUDY 2

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

January 2017 through June 2018 (data collection and follow-up with participants) and continued data analysis from Sept 2017- Sept 2018.

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study

   b. **Study Phase** ☐ **N/A**
   ☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-Comm")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☒ Community-Based Research

5. Is this study a clinical trial? Yes ☐ No ☒

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? N/A

7. Will this study have a billable service? Yes ☐ No ☒

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No _xx__ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:**

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Suchitra Krishnan-Sarin and Stephanie O'Malley	Yale Tobacco Center for Regulatory Science Pilot Grant program	NIH/NIDA 4P50DA036151-04	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☒ Grant-M# **IRES 13-002663** ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

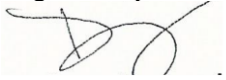
NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Deepa Camenga	Yale	Drp9
Role: Co I	Ralitza Gueorguieva	Yale	rg268
Role: Co I	Suchitra Krishnan-Sarin	Yale	Sk236
Role: RA	Stephanie Dwy	APT	sd596
Role: RA	Skye Orazietti (MAIDEN NAME Skye Peters)	APT	sp537
Role: Statistician	Fanyong Li	Yale	fl86
Role: Study Investigator	Krysten Bold	Yale	kb667
Role: Consultant	Thomas Liss	Yale	tbl3
Role: Data Manager	Elaine LaVelle	Yale	et17

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Deepa Camenga, MD 

12/5/16

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)

X No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)

X No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

Lori Post _____ 12/6/16

Chair Name (PRINT) and Signature Date

Emergency Medicine

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

STUDY 2

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Due to poor recruitment levels with our original study design, we are requesting a revision of the protocol to reflect updated study procedures. As of 9/28/17- we have enrolled one patient in the study who has completed all study procedures. The data for this 1 participant will be analyzed, but not included in the total n for STUDY 2. This participant has completed all study procedures and will not be informed directly that the study 1 has been modified to STUDY 2, as the modification was not due to concern of risk to subjects, rather that a sufficient number of subjects in our local community did not meet eligibility criteria..

Our revised protocol (named STUDY 2), instead of focusing on both naturalistic dual use behaviors and behaviors while switching to e-cigarettes, now is focusing only on the naturalistic behaviors of 32non-treatment seeking young adult e-cigarette/combustible tobacco product dual users. Combustible tobacco products include **cigarettes, cigars, cigarillos, hookah, roll your own cigarettes)**.

In this one-year pilot study of 32 non-treatment seeking young adult e-cigarette/combustible tobacco product dual users (16 males/16 females), we will use smartphone-based ecological momentary assessment (EMA) to gather real-time data of e-cigarette and combustible tobacco product behaviors during a naturalistic 1-week combustible tobacco product/e-cigarette dual use period. (1) Participants will respond to daily random prompts assessing in-the-moment use of e-cigarettes/cigarettes and the subjective factors (ratings of satisfaction and withdrawal) and contextual factors (location, activity, social cues) associated with each episode of use. They will also complete daily electronic diaries to document e-cigarette use episodes/day, amount of e-liquid used, cigarettes smoked/day, nicotine concentrations and flavors used during the day, and how satisfied they were with the e-cigarette experience during the study. They will be queried about whether they changed product constituents (flavors, numbers of flavors, nicotine concentrations). We will also collect markers of carbon monoxide and nicotine exposure (CO, cotinine) throughout the study.

STUDY 2

Aim 1: To determine how within-subject's ratings of subjective factors (withdrawal, satisfaction with tobacco products) change between episodes of e-cigarette use vs. episodes of other combustible tobacco product use (cigarettes, cigars, cigarillos and/or hookah).

> Hypothesis A: Young adult dual users, particularly males, will report lower satisfaction and higher withdrawal scores with episodes of e-cigarette use, in comparison to episodes of combustible tobacco product.

Aim 2: To examine gender differences in e-cigarette use patterns among young adult dual users.

Aim 3: To examine gender differences in e-cigarette use patterns among young adult dual users.
Hypothesis B: Young men will be more likely smoke/vape for the rewarding effects of nicotine.

Hypothesis C: Young women will be more likely to smoke/vape in response to contextual reasons.

Exploratory Aim: To examine sex differences in within-subjects' changes in cotinine levels during the dual use periods.

STUDY 2

2. **Research Plan:**

a. **Overview:** In this one-year pilot study of 32 non-treatment seeking young adult e-cig/combustible tobacco product dual users (15 males/15 females), we will use smartphone-based ecological momentary assessment (EMA) to gather real-time data of e-cigarette and combustible tobacco product behaviors during a 1-week cig/e-cigarette dual use period. Participants will be eligible if they self-report use of e-cigarettes at least one day during the past 7 days and use of at least one other combustible tobacco product at least one day during the past 7 days. Participants will respond to daily random prompts assessing in-the-moment use of e-cigs/combustible tobacco products and the **subjective factors** (ratings of satisfaction and withdrawal) and **contextual factors** (location, activity, social cues) associated with each episode of use. They will also complete daily electronic diaries to document e-cigarette use episodes/day, amount of e-liquid used, combustible tobacco products smoked/day, nicotine concentrations and flavors used during the day, and how satisfied they were with the e-cigarette experience during the study. They will also be queried about whether they changed product constituents (flavors, numbers of flavors, nicotine concentrations). We will also collect markers of carbon monoxide and nicotine exposure (CO, cotinine) throughout the study.

b. **Settings:** We will recruit participants from Southeastern CT (New Haven County, CT; 75% White, 13% Black, 3% Asian; ethnicity: 15% Latino). We expect some participants will be college students from other areas, thus generalizing our findings. Baseline study visits will occur at the APT Foundation, Inc. and follow-up visits may occur at APT, CSRU or public locations (i.e. coffee shops, libraries etc.)

c. **Participants: See Inclusion and Exclusion Criteria**

d. **Procedures:**

Recruitment and Screening: Our team has developed an age-appropriate, targeted strategy for recruitment (see III). Potential participants will be recruited through flyers, targeted advertisements on Facebook, Craigslist, and on public boards in local colleges, and through the Yale Center for Clinical Investigation volunteer database. Screening options will be provided (phone/text, or the Yale Qualtrics online survey system). We are confident we can recruit 3-4 participants/month over 9 months to reach sample size of n=30 32 in 1 year.

Study Entry: We will contact participants who meet inclusion criteria to schedule an in-person assessment at APT Foundation, Inc. Potential participants will meet with the Study Research Associate to be re-screened for eligibility. Women will provide a urine sample to verify pregnancy status. We will collect breath CO and salivary cotinine samples. After obtaining written consent, participants will complete a battery of baseline questionnaires. The RA will ask participants to provide cell, home, and work phone numbers, addresses, and contact information for at least 2 locaters. The RA will notify each participant of the time of their next assessment by text/phone and mail. If after 3 attempts by telephone/text the participant cannot be contacted, the RA will contact the other 2 locators. We will also use this method to contact participants if they have ≥ 24 hours of missing data.

STUDY 2

Participant Training upon Study Enrollment: The RA will teach participants to use the smartphone-based EMA data collection tool and to follow CM procedures. Participants will be instructed to: (1) continue smoking combustible tobacco products ad libitum without changing their smoking frequency/pattern during the study; (2) provide and use their own combustible tobacco products and e-cigarette and liquid during the study. The subjects will be paid for the week of EMA participation and CM-reinforced CO monitor video submissions at the follow-up appointment.

EMA data collection tool: We will use the MetricWire Android and iOS mobile applications ("apps") for EMA data collection.(64) Participants will submit responses to survey questions and upload multimedia via the app. With guidance from the Canadian and U.S. Governments, the app is designed in careful reference to Good Clinical Practice (GCP), including the FDA's part 11 HIPAA regulatory compliance. The app generates random prompts with the ability to set minimal interval time between prompts. Participants will also be prompted to complete daily night-time diaries. *5.1. Quality Checks and Procedures*: Data will be stored on a HIPAA and 21 CFR Part 11 compliant servers and encrypted during transit. Study investigators will have access through an encrypted web-based application. Participant data is uploaded from the mobile app when it is connected to wireless. The RA will check the database daily to complete and correct data entry.

STUDY 2

Contingency management (CM) procedure: On days 1-7, the MetricWire app will randomly prompt participants twice daily (in am and pm) to record a video of them blowing into the CO monitor. They will text/email (via their phone) the video to the study phone/e-mail. To promote video documentation, participants will receive $1 for each on-time, valid video submission; this will continue to increase by $1 per valid video submission for each consecutive daily video submission up to a maximum of $14/day on Day 7 per Table 1. There will be a reset contingency for lack of video submission; participant's payments will be reset to the initial ($2.00/day) amount. The total possible CM payment is $56, and total possible compensation for study participation is $150 (Table 1).

UPDATED Table 1: Study 2 Study Flow and Contingency Management Reinforcement Schedule

WEEK 1	Day 0	1	2	3	4	5	6	7	DAY 8-10	TOTALS
Study visit *	**Baseline study visit ($15)**		**a**						**F/U visit ($15) and payment for EMA**	**$30**
Remuneration for EMA		Participant completed smart-phone based Ecological Momentary Assessments								**$50**
85% EMA completion incentive										**$14**
CO breath test: On-time/valid sample, regardless of the CO value (split for am/pm payment)		$2 ($1/$1)	$4 ($2/$2)	$6 ($3/$3)	$8 ($4/$4)	$10 ($5/$5)	$12 ($6/$6)	$14 ($7/$7)		**$56**
***Study visit activities:** *a) Review EMA procedures via phone*								**TOTAL:**		**$150**

Length of Study Visits

Baseline: 1.5 hours

STUDY 2 Follow-Up (Day 8-10): Up to 30 minutes

e. Primary Outcome: The primary outcomes are daily mean withdrawal scores (measured 3x/day with the Mood and Physical Symptoms Scale) and satisfaction with e-cigarette (measured daily with a 1-10 Likert scale).(65)

STUDY 2

f. Baseline assessments **Demographics:** age, gender, race, ethnicity, and level of schooling completed. **Combustible Tobacco Product Smoking: S**tructured Timeline Follow-Back (TLFB) interviews will document the # of combustible tobacco products smoked per day during the past 28 days.(66) **E-Cigarette Use:** Structured TLFB interviews will document the # of episodes of e-cigarette use per day during the past 28 days. We will also query participants about nicotine concentrations used, flavors used, and the mls of liquid used/day. We already have extensive experience with the collection of these measures from work with adolescent e-cigarette users in the Yale TCORS project. **Nicotine Dependence:** Fagerstrom Test of Nicotine Dependence-R**,** a 6-item scale to estimate the severity of dependence.(67) **Abstinence Self-Efficacy**: The Smoking Self Efficacy Questionnaire to measure self-efficacy.(68) **Preferred Product Features:** Participants will be asked to bring their preferred cigarette and e-cigarette to the baseline visit. We will record the brand/type of cigarette and e-cigarette (brand, nicotine concentration, flavor, battery voltage, tank/cartridge size, propylene glycol/vegetable glycerin ratio).

STUDY 2

g. Time based and Event based sampling procedure (EMA):

Daily Momentary Assessments: Participants will be randomly prompted with the MetricWire app up to 3x daily to provide data on e-cigarette/combustible tobacco product use in the last 15 minutes, the type of e-cigarette/combustible tobacco product used (brand/type), subjective factors (withdrawal) and the contextual factors surrounding the episode. **Subjective factors** will include *Mood* and *Withdrawal*. To maintain brevity during the random prompts, We will use the Mood and Physical Symptoms Scale (MPSS) to measure severity of five withdrawal symptoms (depressed, irritable, restless, hungry and poor concentration) and urge to smoke (craving).(65) Total score ranges from 5 to 25 with a higher score indicating a higher severity of withdrawal symptoms, we will use the International Positive and Negative Affect Schedule Short Form's measures of negative affect.(69) Participants will rate on a 5 point scale their agreement with experiencing the following emotion: (upset, hostile, ashamed, nervous, afraid). **Contextual factors** will include questions about *Companionship* ("During this smoking/vaping episode, who were you around?" (smoker, person who is vaping, non-smoker, alone)), *Location* ("Where were you?" (home, work/school, vehicle, bar/restaurant/store, other)), and *Activity* ("What were you doing?" (eating/drinking a non-alcoholic beverage, drinking alcohol, working/reading/studying, traveling, socializing, other)). Participants will have 30 minutes to respond to random prompts; otherwise data will be considered lost. Each random prompt will be date- and time-stamped and record whether the assessment was completed, missed, delayed, or disbanded. *This method aims to accrue a representative sample of occasions focused on the participants' immediate state.*

STUDY 2

Daily Electronic (e-) Diaries: Participants will fill in daily night-time e- diaries via the app to provide data on e-cigarette use (episodes of e-cigarette use/ day) and combustible tobacco product smoking (# combustible tobacco products smoked/day). They will provide a rating of satisfaction with the e-cigarette they used during the day, and overall satisfaction rating of using their e-cigarette (1-10 Likert scales). Participants will record pictures of the e-cigarette(s) used during that day via the MetricWire app and provide a description of features. *We have chosen daily night-time e-diaries to minimize participant burden.*

STUDY 2

h. In-person study visits: In-person visits will occur in public places or study offices at baseline and follow-up. In addition to the CM procedures for CO monitor video submission, saliva cotinine samples will be collected at baseline, and follow-up to explore changes in cotinine levels.

3. Genetic Testing N/A ☒

4. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

STUDY 2

We plan to recruit 32 non-treatment seeking young adult e-cig/cigarette dual users (15 males/15 females), who use both e-cigarettes and combustible tobacco products. See V.7 for Inclusion/Exclusion Criteria.

5. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decision ally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

6. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

STUDY 2

Inclusion Criteria. Each participant must:

(1) be 18 through 29 years of age;
(2) **use at least one type of combustible tobacco product (cigarettes, cigars, cigarillos, hookah, roll your own cigarettes) on at least 1 day during the past 7 days (DURING the PAST 7 days, on how many days did you use a combustible tobacco product ? (1 or more)**
(3) use e-cigarettes on at least one day during the past 7 days
4) have access to an e-cigarette

(5) fluent in English;
(6) have a functioning cell phone for personal use with wireless, camera, and application (via Apple or Android platform) capability;
(7) have access to wireless networks at least once daily;
(8) have self-reported good health.

Exclusion Criteria. Participants who: (1) report serious medical illness; (2) are enrolled in a substance abuse or smoking cessation program/research study;(3) are interested in using smoking cessation pharmacotherapy during the study (to isolate effects of e-cigarette from pharmacotherapy); (4) take any psychoactive medications; (5) are women who are currently/planning to be pregnant or breastfeeding.

7. How will **eligibility** be determined, and by whom?

Participants who are potentially interested in participating will have three methods to contact the study

1. Eligibility can be determined via use of a screening from by the PI/RA with the subject during in person recruitment.
2. Potential participants can elect to be screened via phone. In this case, eligibility can be determined via phone by use of a screening form by the PI/RA.
3. Potential participants can elect to screened via an online Qualtrics form. In this case the RA/PI will review the responses in Qualtrics to determine eligibility
4. Potential participants can elect to be screened via text. In this case potential participants will be informed that text communication is vulnerable to breach of confidentiality.

8. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The potential risks in this study are related to:

1. Risks Associated with Rating Scales and Assessments Risks from the rating scales and assessments, self-reports, and interviews are not beyond usual research procedures. Research assessments are all non-invasive, and should add no risk. The major disadvantages are the time taken to complete them and possible breach of confidentiality. The rating scales and structured assessments are all non-invasive and have been utilized in clinical studies with no known negative outcomes and should also

add no risks to subjects, as our past experience indicates. Our past experience with these measures indicates that they are acceptable to subjects. Any potential risks (e.g., discussion of upsetting events), however, will be minimized through the use of a trained, experienced Research Associates, supervised by Drs. Camenga and Krishnan-Sarin. All adverse events will be immediately reported to the PI by research staff.

STUDY 2

2. Breath and saliva Collection - Participants will have breath samples taken to measure CO at baseline and follow-up. Testing will be performed by a trained research associate with the Bedfont PICO-Smokerylzer® breath CO monitor (Bedfont Scientific Ltd., Rochester, UK). There are no known risks associated with this test. Subjects exhale into a disposable plastic mouthpiece attached to the monitor; there should be no risk of infection. Saliva collection for cotinine is non-invasive.

3. Risks Associated with Loss of Confidentiality The main risk associated with the study is the possibility that confidential information obtained during the study will be disclosed. All efforts will be made to protect subjects' confidentiality. The alternative to participation is for a potential subject to decide NOT to participate. Confidentiality of the results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Project Director.

STUDY 2

4. **Use of electronic cigarette**: Participants will be current combustible tobacco product smokers who have experience with e-cigarettes. The electronic cigarette delivers nicotine in much the same way that a regular cigarette does, through inhalation. **Participants will provide and use their own e-cigarettes (including all components, parts and accessories, and e-liquids (including flavorings) during this study.**
    i. Nicotine exposure: The participants are required to be current combustible tobacco product smokers, and are, therefore, already self-administering nicotine. Nicotine intake during pregnancy may be associated with increased risk for spontaneous abortion, increased perinatal mortality and with low infant birth weights. We will exclude females who are pregnant/planning to become pregnant or nursing from this study.
    ii. The most frequently reported adverse events reported in a clinical trials and cohort studies of e-cigarettes included cough, dry mouth, shortness of breath, throat irritation, and headache.(70) Other adverse events may include nausea and stomach cramps. Several studies have noted that the reported adverse events were classified as mild.
    iii. A 2016 Cochrane Review of 3 RCTs and 21 cohort studies found that none of the studies reported serious adverse events considered related to electronic cigarette use. The most frequently reported AEs were mouth and throat irritation, most commonly dissipating over time.

9. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Protections Against Risks include:

1. Inclusion and exclusion criteria and the use of a trained research associate will help to avoid the enrollment of subjects into this study who are either ineligible or who would be at greater risk for complications because of psychiatric, or medical illnesses.
2. All patient interactions will be conducted in areas that are as private as possible in the clinic (APT) or public setting.
3. Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Computerized subject data will be password protected. All identifiable information will be stored in a locked research cabinet in a locked until. All subjects will be assigned a study subject number. Subsequently, subjects will be identified in the Case Report Forms (CRFs) only by that number and an encoded version of their initials (i.e., John Doe = JDO). A list of numbers and the corresponding names will be maintained by the Project Director.
4. Any identifiable information that is obtained in connection with this study will be disclosed only with subject permission or as required by U.S. or State law. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996. We will clearly explain our mandated obligation to report incidents, including suspicion of child or elder abuse or neglect, threats of harm to self and others. Data will only be reported in aggregate. During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly adhere to the rules of confidentiality. Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the Project Director, until they are destroyed, after all analyses are complete and after the federal requisite waiting period (7 years) to maintain records. Any information published as a result of the study will be such that it will not permit identification of any subject.
5. **Protection of the health-related information collected via MetricWire**
   MetricWire is a cloud-based data collection and analytics platform. The MetricWire platform provides users with the ability to log, analyze, and visualize data collected from smartphones, tablets and the web. The MetricWire system includes the following components which will transmit PHI:

   Mobile Applications: MetricWire provides Android and iOS mobile applications that allow participants to view study details, submit responses to survey questions and upload multimedia. This application will be used to collect daily momentary assessments during the study. The Android Mobile application is a native application written in Java using the Android Software Development Kit (SDK) provided by Google, the creators of Android. The iOS Mobile application is a native application written in Objective--C using the Apple Software Development Kit (SDK) provided by Apple, the creators of iOS. Data is encrypted and transferred from the app to the server when the smartphone is connected to wireless networks.

   Participant Portal: The Participant Portal is a web application that allows participants to submit responses to survey questions and upload multimedia. Participant will have the option

to complete the daily nighttime assessments via this portal. The Participant Portal is accessed at my.metricwire.com.

Research Portal: The Research Portal is a web application that is used by the study investigators to design and deploy studies to mobile devices and the web. The Research Portal is accessed via research.metricwire.com.

Data Security: Through the Metric Wire's Notice of Privacy Practices ("Privacy Notice") individuals are informed of the Company's legal duties and these Policies and Procedures, as well as their individual rights with respect to their Protected Health Information.(71) The data obtained from the MetricWire app is stored on Health Insurance Portability and Accountability Act (HIPAA) and 21 CFR Part 11 compliant servers and it is encrypted during transit. All employees of MetricWire must adhere to HIPAA. Researchers can access the data at any time in real time via the web-based Research Portal. MetricWire supports symmetric AES---128, AES---192 and AES---256 based on the organization's preference for data storage. If mandated, asymmetric encryption can be implemented for the data storage. All symmetric keys are encrypted using the Scrypt Key Derivation function and stored in HMAC---SHA256. The passwords and data is encrypted using TLS v1, 1.1 or 1.2(based on the latest protocol the user's browser supports) in transit.(72)

The resulting database will be property of the Yale University investigators. This data and any kind of logs, will be kept in a secure HIPAA compliant database stored at Yale School of Medicine. This server is firewall and password protected, with limited access only to investigators.

10. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? **MINIMAL RISK**
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? **N/A**
    c. Include an appropriate Data and Safety Monitoring Plan.
    d. For multi-site studies for which the Yale PI serves as the lead investigator: **N/A**
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
        ii. What provisions are in place for management of interim results?
        iii. What will the multi-site process be for protocol modifications?

Monitoring for data integrity and safety will be the responsibility of the investigators and the Yale Human Investigation Committee (HIC). The principal investigator will be responsible for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the specified frequency of the reviews at a minimum of every 6 months (including when reapproval

of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator or the HIC have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed minimal. Although we have assessed the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study from http://www.yale.edu/hrpp/forms-templates/biomedical.html for Minimal risk.

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, Reportable Adverse Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings, and via email as they are reviewed by the principal investigator. The protocol's research monitor(s), funding agencies, and regulatory and decision-making bodies will be informed of severe adverse events within 5 days of the event becoming known to the principal investigator.

STUDY 2

11. **Statistical Consideration:** Describe the statistical analyses that support the study design.

Data analysis will be conducted with SAS (Cary, NC) by *Drs. Gueorguieva and Bold (*Co-I) and the Yale Center for Analytic Sciences. Effect size estimates with 95% CIs will be constructed for each Aim to inform future studies.

Overview: This is an observational study of e-cigarette and combustible tobacco product use in young adults. Data analysis will be conducted in collaboration with *Ralitza Gueorguieva, PhD* (Co-I) and the Yale Center for Analytic Sciences. We will conduct all analyses with the latest version of SAS (Cary, NC) software. We will calculate descriptive statistics prior to statistical analyses and evaluate data distributions of continuous predictors. If data are approximately normally distributed or can be transformed to normality, we will use linear mixed models for statistical analysis. Generalized linear mixed models will be used for non-normal data (e.g.

logistic mixed models for binary data; negative binomial or Poisson mixed effects models for count data). Effect size estimates with 95% CIs will be constructed for each specific aim to inform future studies.

a. Justification of Sample Size: Estimation of sample size (n=32) is based on achieving a clinically meaningful precision in effect size estimates for the primary outcome of interest. With 30 subjects we will be able to construct a 95% CI for the mean change in e-cigarette episodes/day from week 1 to 2 of width up to 0.37 standard deviations away from the mean (Aim 1) and 95% CI for the slopes of the regression relationships in Aim 2 of half-widths up to approximately 0.67 of the corresponding slope values. The obtained interval estimates will be used to inform future larger definitive studies.
   Analysis Plan: Aim 1 will determine how within-subject's ratings of subjective factors (withdrawal, satisfaction with tobacco products) change between episodes of e-cigarette use vs. episodes of other combustible tobacco product use (cigarettes, cigars, cigarillos and/or hookah)

   During e-cigarette and combustible tobacco product use periods. We will evaluate the variability in levels of satisfaction and withdrawal scores during these periods. Correlations between repeated measures on an individual will be modeled with random subject effects. Aim 2 will evaluate gender differences in e-cigarette use patterns among young adult dual users mean changes in e-cigarette use between the dual use and exclusive e-cigarette use period that differ by sex. We will evaluate changes in contextual factors and will assess effect sizes and construct 95% CIs for change in e-cigarette use

12. Data Management:

Quantitative outcomes will be collected using paper forms which will be double entered into a secure database. Error checking and data validation will occur weekly and any problems will be queried and resolved immediately. Dr. Camenga will create monthly data quality reports to check for completeness and accuracy of key variables, as well as rates of recruitment, retention, and follow-up. Baseline demographics and smoking behaviors will be summarized. Continuous data will be expressed as mean values with standard deviations and categorical data will be presented as counts with percentages.

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol_32

b. If this is a multi-site study, give the total number of subjects targeted across all sites___

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☒ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review*	☒ Departmental/Center Research Boards	☒ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☒ YCCI Recruitment database	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	

☐ Other (describe):

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Through our previous studies, our team has developed an age-appropriate, targeted strategy for recruitment. Potential participants will be recruited through flyers, advertisements on Facebook (targeted to 18-through 29-year-olds in CT), craigslist, and on public boards in New Haven, and through the Yale Center for Clinical Investigation volunteer database. Screening options will be provided.

b. Describe how potential subjects are contacted.

Potential participants can contact the study to determine eligibility through the following methods:

1. Phone call: Potential subjects can call the study PI via the phone number listed on the recruitment materials at be screened via phone and schedule an intake appointment if eligible.
2. Text: Potential subjects can text the word STUDY to the study text number 203-376-4459 listed on the recruitment materials. When they do this they will receive a link to the Qualtrics screening eligibility questionnaire (Appendix DD)
3. Potential participants can scan a QR code or enter a website bitlink that will direct them to a Yale Qualtrics website wherein subjects learn information about the study and can elect to contact the study via fill out the Qualtrics Screening Form or to call the study number.
4.

Procedure to schedule study visit for eligible participants:

If they are found to be eligible they will be asked whether they would like to be contacted via text/phone to schedule an intake appointment. The RA/PI will then text/call the potential subject to schedule an intake. **Given the breadth of screening procedures used, at the onset of the intake appointments, subjects will be rescreened to ensure study eligibility prior to consent.**

c. Who is recruiting potential subjects?

The PI or a research assistant will recruit potential subjects.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☒ Social Security numbers – for participant reimbursement card

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

Additional health measures for screening will include:

Combustible tobacco product smoking history
E-cigarette use history
Health Status (self-reported)
Enrollment in substance use/smoking cessation program/research study.
Interest in using smoking cessation medications
Medication history (use of any psychoactive medication)
For Women: Pregnancy status, current/plan for pregnant or breastfeeding

5.Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐ Yes, all subjects
☒ Yes, some of the subjects (POTENTIAL RELATIONSHIP)
☐ No
If yes, describe the nature of this relationship. Deepa Camenga, MD is pediatrician who provides clinical care at the Adolescent Clinic at the Yale New Haven Hospital primary Care Center. There is a potential risk that an eligible participant may have received care from Dr. Camenga in the Primary Care Center, however this study does not recruit directly from the Primary Care Center and participation in the study will not affect the nature of the treatment the participants receive in the PCC.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:
☐ For entire study
☒ For recruitment purposes only
☐ For inclusion of non-English speaking subject if short form is being used **and a translated HIPAA research authorization form is not available on the University's HIPAA website**

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

Consent waiver will be requested for initial patient screening via telephone and Yale Qualtrics survey (Via text or web), done only to determine subject eligibility. We request a waiver for HIPAA authorization to obtain their phone number for voice and text and/or email as this method is equivalent to having a person leave their phone number on a voice mail and is being used to attract young adults to contact the research team.

Participants will provide verbal consent for the screening process and this consent is also included in the Qualtrics screening eligibility survey.

7. After eligibility has been decided, written consent will be requested from all participating subjects upon enrollment. It would be impractical to obtain written consent and consent for HIPAA authorization for phone screening procedures as screening will be done on the phone, text, or web

   By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☒ Compound Consent and Authorization form
   - ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   Deepa Camenga, Thomas Liss, RA- Stephanie Dwy and Skye Orazietti (Maiden Name Skye Peters).

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   After the screening process is complete and subject is found to be eligible, the RA/PI will schedule them for an in person intake. At this intake, all eligible participants will be asked for written consent using the Yale HIC approved combined consent/HIPAA form. All eligible participants will also be asked to provide contact information in the following manner. In addition to providing their own personal contact information, participants will be asked to give the names of two friends or relatives whom we can contact to obtain this information. We will contact these individuals only if we are unable to contact the participant directly and then only for the purpose of obtaining forwarding address and phone number. We will inform the person that the participant has authorized us to contact them and they will be asked if they are willing to give out this information. If they decline, they will not be contacted again. The participant will be advised that these people that you have given us their name and information so if we need to call them they are already aware. Participants will be given the option to list a contact person from an office/clinic that they attend for medical are. If they choose to list this contact, we will ask the participant to

sign a release so we can call the office/clinic if we have difficulty finding the participant for follow-up interviews. If the participant is unable to complete an in-person or phone interview, we may send them a follow-up questionnaire with a self-addressed, stamped envelope. If they are unable to come to the clinic but are willing to complete an interview we will meet the participant at a public place to collect a breath carbon monoxide sample and salivary cotinine sample, and questionnaire data.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Through the verbal interaction with the potential subject, the PI or research assistant will make an assessment of the subject's ability and capacity to consent to the research. Participants must be young adults, therefore we do not expect that they will be a higher than usual risk of having fluctuating, limited, or diminishing decision-making capacity during the course of the research study,

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Yale HIC-approved compound consent and authorization form and a separate written permission to allow videotaping.

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

N/A- Non-English speaking subjects do not meet inclusion criteria

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒ **Not Requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☒ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☒ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. How will the research data be collected, recorded and stored?

Research data will be collected from study subjects by the PI or trained Research Associates (RA) who has successfully completed all required HIC and HIPAA training, using the paper study forms approved by Yale HI. Subjects will also be able to complete these same forms via a laptop as a survey administered through the Yale Qualtrics program These forms will only include the subject's unique identifier, which is assigned to the subject at the time of enrollment, to which only study researchers will have access.

See V.10.5. for description of data security plan for MetricWire app.

All information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. All collected data will be stored in locked files, in the locked study-dedicated office of the Principal Investigator, with access granted only to the study research team. Paper data will be computerized (entered into a study database) and password protected, with access granted only to the study research team. Data will only be reported in aggregate. Data will be deidentified prior to formal data analysis, making individual subject identification impossible.

b. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

c. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
All portable devices must contain encryption software, per University Policy 5100. *If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url* http://its.yale.edu/egrc or email it.compliance@yale.edu

Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Moveable devices will be encrypted to protect identifiable information, following University policy. Only study researchers will have access to the link between subject name and identifier.

d. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. Data will be de-identified prior to formal data analysis, making individual subject identification impossible.

Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI, investigators and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the PI, until they are destroyed, after all analyses are complete. At that time, all data will be destroyed using an approved method as performed by, or with the assistance of ITS Med.

e. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Only the PI, investigators and study personnel will have access to the data which will be kept securely on a password-protected server.

During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly follow rules of confidentiality.

f. If appropriate, has a Certificate of Confidentiality been obtained?
We will not obtain a certificate of confidentiality

g. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g., HIV testing – reporting of communicable diseases; parent interview - incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

NO

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

This study does not provide direct benefits to the participant. Although the proposed research poses minimal risks to participants, the benefits to scientific knowledge are numerous. The results from this study may help scientists understand how young men and women switch from cigarettes to e-cigarettes.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

The alternative to participating in the proposed study is to not participate.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Participants will receive payments per the schedule below (and Table 1)

STUDY 2

- $15 for each in person study visit ($30 total)
- $50 for completion of the EMA procedures
- Up to $14 for completion of 85% of more of the EMA prompts
- Up to $56 for on-time and valid video recordings of breath CO measurement
- TOTAL Possible payment=$150 (of which $56 is earned through CM)

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

Subjects will be responsible for the costs associated with:

1. Purchasing their e-cigarette, e-liquid, or any other e-cigarette product components.
2. Transportation to and from study visits
3. Operating their cell phone

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

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a. Will medical treatment be available if research-related injury occurs?
b. Where and from whom may treatment be obtained?
c. Are there any limits to the treatment being provided?
d. Who will pay for this treatment?
e. How will the medical treatment be accessed by subjects?

Subjects who develop a mental or physical problem as a result of involvement in this study, will have appropriate treatment arranged. The subject's insurance carrier will be expected to pay the costs of such treatment. No financial compensation is available for this treatment.

REFERENCES CITED

[1] Krishnan-Sarin S, Duhig AM, McKee SA, et al. Contingency management for smoking cessation in adolescent smokers. Exp Clin Psychopharmacol 2006;14:306-310.
[2] U.S Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon Generall. Atlanta, GA: U.S Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
[3] U.S. Department of Health and Human Services. The Health Consequences of Smoking--50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014; 2014.
[4] Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.
[5] Edwards SA, Bondy SJ, Callaghan RC, et al. Prevalence of unassisted quit attempts in population-based studies: a systematic review of the literature. Addict Behav 2014;39:512-519.
[6] Curry SJ, Sporer AK, Pugach O, et al. Use of tobacco cessation treatments among young adult smokers: 2005 National Health Interview Survey. Am J Public Health 2007;97:1464-1469.
[7] Guiney H, Li J, Walton D. Barriers to successful cessation among young late-onset smokers. The New Zealand medical journal 2015;128:51-61.
[8] Richardson A, Pearson J, Xiao H, et al. Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. Am J Public Health 2014;104:1437-1444.
[9] Schmidt L, Reidmohr A, Harwell TS, et al. Prevalence and reasons for initiating use of electronic cigarettes among adults in Montana, 2013. Prev Chronic Dis 2014;11:E204.
[10] Pepper JK, Ribisl KM, Emery SL, et al. Reasons for starting and stopping electronic cigarette use. Int J Environ Res Public Health 2014 11:10345-10361.
[11] Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. Nicotine Tob Res 2015;17:127-133.
[12] Czoli CD, Hammond D, White CM. Electronic cigarettes in Canada: prevalence of use and perceptions among youth and young adults. Canadian journal of public health = Revue canadienne de sante publique 2014;105:e97-e102.
[13] Choi K, Forster J. Characteristics associated with awareness, perceptions, and use of electronic nicotine delivery systems among young US Midwestern adults. Am J Public Health 2013;103:556-561.
[14] Kong G, Morean ME, Cavallo DA, et al. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults [published online ahead of print Dec 6 2014]. Nicotine Tob Res 2015;17:847-854.
[15] Camenga DR, Kong G, Cavallo D, et al. Predictors of Youth Use of E-cigarettes for Smoking Cessation. College on Problems of Drug Dependence. Phoenix, AZ, 2015:24.
[16] Grana RA, Ling PM. "Smoking revolution": a content analysis of electronic cigarette retail websites. Am J Prev Med 2014;46:395-403.

[17] Curry SJ, Sporer AK, Pugach O, et al. Use of Tobacco Cessation Treatments Among Young Adult Smokers: 2005 National Health Interview Survey. Am J Public Health 2007;97:1464-1469.
[18] Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control 2014;23 Suppl 3:iii3-9.
[19] Giovenco DP, Hammond D, Corey CG, et al. E-Cigarette Market Trends in Traditional U.S. Retail Channels, 2012–2013. Nicotine Tob Res 2014.
[20] Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. Prev Med 2014;69:248-260.
[21] McRobbie H, Bullen C, Hartmann-Boyce J, et al. Electronic cigarettes for smoking cessation and reduction. The Cochrane database of systematic reviews 2014;12:Cd010216.
[22] Litt MD, Duffy V, Oncken C. Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. Tob Control 2016: pii: tobaccocontrol-2016-053223.
[23] Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382:1629-1637.
[24] Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. PloS one 2013;8:e66317.
[25] Tseng TY, Ostroff JS, Campo A, et al. A Randomized Trial Comparing the Effect of Nicotine Versus Placebo Electronic Cigarettes on Smoking Reduction Among Young Adult Smokers. Nicotine Tob Res 2016;18:1937-1943.
[26] Kalkhoran S. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med 2016;4:116-128.
[27] Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. Bmj 2004;328:1519.
[28] Tian J, Venn AJ, Blizzard L, et al. Smoking status and health-related quality of life: a longitudinal study in young adults. Quality of Life Research 2015.
[29] Lopez AA, Eissenberg T. Science and the evolving electronic cigarette. Prev Med 2015;80:101-106.
[30] Grace RC, Kivell BM, Laugesen M. Gender differences in satisfaction ratings for nicotine electronic cigarettes by first-time users. Addict Behav 2015;50:140-143.
[31] Oncken CA, Litt MD, McLaughlin LD, et al. Nicotine concentrations with electronic cigarette use: effects of sex and flavor. Nicotine Tob Res 2015;17:473-478.
[32] Tackett AP, Lechner WV, Meier E, et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. Addiction 2015;110:868-874.
[33] Roberts ME, Bidwell LC, Colby SM, et al. With Others or Alone? Adolescent Individual Differences in the Context of Smoking Lapses. Health Psychol 2015.
[34] Shiffman S. Relapse following smoking cessation: A situational analysis. J Consult Clin Psychol 1982;50:71-86.
[35] Myers MG, Gwaltney CJ, Strong DR, et al. Adolescent First Lapse Following Smoking Cessation: Situation Characteristics, Precipitants and Proximal Influences. Addict Behav 2011;36:1253-1260.
[36] McKennell AC. Smoking Motivation Factors. British Journal of Social and Clinical Psychology 1970;9:8-22.
[37] Brandon TH. Negative Affect as Motivation to Smoke. Curr Dir Psychol Sci 1994;3:33-37.

[38] Shiffman S, Gnys M, Richards TJ, et al. Temptations to Smoke after Quitting: A Comparison of Lapsers and Maintainers. Health Psychol 1996;15:455-461.
[39] Shiffman S, Paty JA, Gnys M, et al. First lapses to smoking: Within-subjects analysis of real-time reports. J Consult Clin Psychol 1996;64:366-379.
[40] Baer JS, Kamarck T, Lichtenstein E, et al. Prediction of smoking relapse: analyses of temptations and transgressions after initial cessation. J Consult Clin Psychol 1989;57:623-627.
[41] Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology 2014;231:401-407.
[42] Spindle TR, Breland AB, Karaoghlanian NV, et al. Preliminary Results of an Examination of Electronic Cigarette User Puff Topography: The Effect of a Mouthpiece-Based Topography Measurement Device on Plasma Nicotine and Subjective Effects. Nicotine Tob Res 2015;17:142-149.
[43] Bullen C, Williman J, Howe C, et al. Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. BMC Public Health 2013;13:210.
[44] Lechner WV, Meier E, Wiener JL, et al. The comparative efficacy of first- versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. Addiction 2015;110:862-867.
[45] Higgins ST, Kurti AN, Redner R, et al. A literature review on prevalence of gender differences and intersections with other vulnerabilities to tobacco use in the United States, 2004-2014. Preventive medicine 2015;80:89-100.
[46] Rath JM, Villanti AC, Williams VF, et al. Correlates of current menthol cigarette and flavored other tobacco product use among U.S. young adults. Addict Behav 2016;62:35-41.
[47] Perkins KA, Jacobs L, Sanders M, et al. Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. Psychopharmacology 2002;163:194-201.
[48] Perkins KA, Karelitz JL. Sex differences in acute relief of abstinence-induced withdrawal and negative affect due to nicotine content in cigarettes. Nicotine Tob Res 2015;17:443-448.
[49] Pineiro B, Correa JB, Simmons VN, et al. Gender differences in use and expectancies of e-cigarettes: Online survey results. Addict Behav 2016;52:91-97.
[50] Doran N. Sex differences in smoking cue reactivity: Craving, negative affect, and preference for immediate smoking. Am J Addict 2014;23:211-217.
[51] Perkins KA. Sex differences in nicotine reinforcement and reward: Influences on the persistence of tobacco smoking. Nebraska Symposium on Motivation, 2009:143-169.
[52] Stone AA, Shiffman S. Ecological momentary assessment (EMA) in behavorial medicine. Ann Behav Med 1994;16:199-202.
[53] Shiffman S, Hufford M, Hickcox M, et al. Remember that? A comparison of real-time versus retrospective recall of smoking lapses. J Consult Clin Psychol 1997;65:292-300.
[54] Rancourt D, Leahey TM, LaRose JG, et al. Effects of weight-focused social comparisons on diet and activity outcomes in overweight and obese young women. Obesity 2015;23:85-89.
[55] Shrier LA, Scherer EB. It depends on when you ask: motives for using marijuana assessed before versus after a marijuana use event. Addict Behav 2014;39:1759-1765.
[56] Thrul J, Buhler A, Ferguson SG. Situational and mood factors associated with smoking in young adult light and heavy smokers. Drug Alcohol Rev 2014;33:420-427.
[57] Huh J, Shin H, Leventhal AM, et al. Momentary negative moods and being with friends precede cigarette use among Korean American emerging adults. Nicotine Tob Res 2014;16:1248-1254.

[58] Setodji CM, Martino SC, Scharf DM, et al. Quantifying the persistence of pro-smoking media effects on college students' smoking risk. J Adolesc Health 2014;54:474-480.
[59] Nock MK, Prinstein MJ, Sterba SK. Revealing the form and function of self-injurious thoughts and behaviors: A real-time ecological assessment study among adolescents and young adults. J Abnorm Psychol 2009;118:816-827.
[60] Shiffman S, Engberg JB, Paty JA, et al. A day at a time: predicting smoking lapse from daily urge. J Abnorm Psychol 1997;106:104-116.
[61] Shiffman S, Hickcox M, Paty JA, et al. Individual differences in the context of smoking lapse episodes. Addict Behav 1997;22:797-811.
[62] Carpenter M. A Randomized Trial of E-cigarettes: Natural Uptake, Patterns, and Impact of Use. Available at: http://projectreporter.nih.gov/project_info_description.cfm?aid=8898038&icde=26164944&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC Accessed August 30 2015.
[63] Morean ME, Kong G, Camenga DR, et al. Contingency management improves smoking cessation treatment outcomes among highly impulsive adolescent smokers relative to cognitive behavioral therapy. Addict Behav 2015;42:86-90.
[64] MetricWire: Breakthrough Research. Available at: https://metricwire.com/ Accessed Oct. 30 2015.
[65] West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology (Berl) 2004;177:195-199.
[66] Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. Measuring alcohol consumption: Psychosocial and biochemical methods. Totowa, NJ: Humana Press, 1992:41-72.
[67] Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. British Journal of Addiction 1991;86:1119-1127.
[68] Etter J-F, Bergman MM, Humair J-P, et al. Development and validation of a scale measuring self-efficacy of current and former smokers. Addiction 2000;95:901-913.
[69] Thompson ER. Development and Validation of an Internationally Reliable Short-Form of the Positive and Negative Affect Schedule (PANAS). J Cross Cult Psychol 2007;38:227-242.
[70] Hartmann-Boyce J, McRobbie H, Bullen C, et al. Electronic cigarettes for smoking cessation. The Cochrane database of systematic reviews 2016;9:CD010216.
[71] MetricWire Inc. MetricWire 2015 Policies and Procedures. Ontario, Canada; 2015.
[72] DeSouza C. Data Privacy & Security. Ontario, Canada: MetricWire, Inc.; 2015.
[73] Hufford MR. Special methodological Challenges and Opportunities in Ecological Momentary Assessment. In: Stone AA, Shiffman S, Atienza AA, et al., eds. The Science of Real Time Data Capture. New York, NY: Oxford University Press, 2007:54-75.