YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/index.html. Submit the original application and two (2) copies of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY** DATE STAMPED-RECEIVED PROTOCOL NUMBER 1008007245

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Ecological Momentary Assessment and Attentional Retraining for Postpartum Smoking Relapse: A Pilot Study			
Principal Investigator: Ariadna Forray, MD		**Yale Academic Appointment:** Associate Professor	
Campus Address: 40 Temple Street, Suite 6B, New Haven, CT 06510			
Campus Phone: 764-8620	**Fax:**	**Pager:**	**E-mail:** ariadna.forray@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone:	**Fax:**	**E-mail:**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Does the principal investigator, co-investigator, or any research team member obtaining consent, or any of their family members (spouse, child, domestic partner) have an incentive or interest, financial or otherwise, that may be viewed as affecting the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? See Disclosures and Management of Personal Interests in Human Research http://www.yale.edu/hrpp/policies/index.html#COI

□ Yes x No
If yes, list names of the investigator or person obtaining consent:

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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 Cancer Center
- ☒ Yale-New Haven Hospital
- ☐ Specify Other Yale Location: PMS and Perinatal Psychiatric Research Program
- ☐ PET Center
- ☐ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Cancer Data Repository/Tumor Registry

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☐ Connecticut Mental Health Center
- ☐ Veterans Affairs Hospital, West Haven
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Other Locations, Specify:

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:
- ☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
- ☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
- ☐ Dept. of Lab Medicine request for services or specimens form

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.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 8/1/2010 – 7/31/2016; second wave with additional funding 10/1/2018-6/30/2022 (no cost extension)

3. **Targeted Enrollment:** What is the number of subjects

a. targeted for enrollment at Yale for this protocol? 30 (original), an additional 50 in second wave

If this is a multi-site study, what is the total number of subjects targeted across all sites?

b. expected to sign the consent form? 30 (original), an additional 65 in second wave

c. expected to complete some or all interventions for this protocol? 30 (original), an additional 50 in second wave

4. **Research Type/Phase: (Check all that apply)**

a. Study Type

- ☒ Single Center Study
- ☐ Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐

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☐ Coordinating Center/Data Management
☐ Other:

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

c. **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-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study required to be registered in a public database? Yes ☐ No ☒
If yes, where is it registered?
Clinical Trials.gov registry ☐
Other (*Specify*)

6. Will this research study utilize clinical care services at Yale New Haven Hospital or YMG?
Yes ☒ No ☐
If yes, might these be billable to the subject, the sponsor, grant or other third party payer?
Yes ☐ No ☒
If you answered "yes", please register this study in the IDX/GE system at
http://ycci.yale.edu/comply/billing_idxge.html

7. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes _X__ No____ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No

c. Will a novel approach using existing equipment be applied? No

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

Funding Source: Please see IRES-IRB.
1. **Research Team:** Please see IRES-IRB

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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.

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.

PI Name (PRINT) and Signature — Date: 8/10/10

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- 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.
- The student investigator will obtain approval for this research study and any subsequent revisions. Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator 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 forth by the University and qualify to serve as the faculty advisor of this project.

Advisor Name (PRINT) and Signature — Date

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.)
☐ 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, and I agree to submit the Protocol-Specific Conflict of Interest Disclosure Form.
☐ 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.

_____ _____
Chair Name (PRINT) and Signature Date

_____
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 submit a Protocol-Specific Conflict of Interest Disclosure Form 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 had the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

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SECTION V: RESEARCH PLAN

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

Specific Aims

Specific Aim #1: To examine the relapse process in postpartum smokers using Ecological Momentary Assessment (EMA).

Specific Aim #2: To determine the impact of situational and affective stimuli on relapse in the postpartum period.

Specific Aim #3: To examine whether attentional (AR) delivered on a smartphone can modify attentional bias to smoking-related stimuli and craving for tobacco cigarettes.

***Hypothesis #3*:** Women randomized to AR, as compared to those in the attentional control group, will a) show less attentional bias toward smoking-related stimuli, and b) show a decrease in self-reported craving.

Specific Aim #4: To examine whether AR delivered on a smartphone can modify attentional bias to stress-related stimuli and reduce perceived stress.

Hypothesis #4: Women randomized to AR, as compared to those in the attentional control group, will a) show less attentional bias toward stress-related stimuli, and b) show a decrease in self-reported stress.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

The Postnatal Period Presents a Unique Opportunity and Challenge for Smokers

Among the 45 million smokers in the US, pregnancy and the postpartum period presents unique opportunities and challenges. Close to half of women who were smokers prior to conception are able to quit smoking in pregnancy,[1] but nearly 80% of this group relapses within a year after delivery, designating pregnancy as a period of "suspended smoking."[2] Smoking in the mother is associated with increased risks for cancer, heart disease, and chronic pulmonary disease. Postpartum smoking may lead to continued smoking into the next pregnancy with associated harm to the fetus and the newborn. Equally deleterious are the health effects of second-hand smoke on newborns, which include increased risk for respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction and cognitive impairment.[3] In addition, women who smoked pre-pregnancy have less intent to breastfeed[4] or cease breastfeeding early in order to restart smoking.[5] Thus, understanding the underlying triggers for relapse in the postpartum period is crucial in ensuring abstinence and creating interventions for women that relapse.

Abstinence, Relapse and Ecological Momentary Assessment (EMA)

One of the major challenges to abstinence is the frequent episodes of intense cravings that arise due to affective or situational stimuli.[6] These episodes of intense craving are high-risk periods that often lead to smoking. Most lapses progress to relapse[7] and the failure abstinence. For this reason it is crucial to study relapse processes in people's natural environments. EMA is particularly appropriate for studying the relapse process, because it provides repeated sampling of real-world events, as they are influenced by environmental and situational cues. The use of EMA allows for the study of dynamic changes in behavior over time and across situations.[8] To our knowledge, EMA has not been previously used to study smoking relapse in this unique patient population.

The Role of Mood Symptoms in Smoking Relapse Among Perinatal Women

Affective experience has long been considered central to smoking, and stress and negative affect (NA) have been considered major drivers of relapse.[9] Some evidence suggests that, as in a number of other populations,[10-12] depressive symptoms moderate smoking outcomes in perinatal women.[13-16] Stress and dysphoria can be particularly problematic for postpartum women. Recently, Cinciripini and colleagues found that behavioral therapy stabilized mood and increased abstinence rates among postpartum smokers with depressive symptoms.[14] The behavioral therapy did not benefit euthymic smokers supporting a moderating role for depression and a need to monitor mood among postpartum women with lifetime smoking.

Attentional Bias and Smoking.

Remaining abstinent is an active process that requires attention to avoid slips and lapses. When active processes are insufficient or cravings are overwhelming, lapses and relapses occur. Automatic processes, such as attentional bias contribute to the relapse process. Consistent with a classical conditioning paradigm, attentional bias in addictive behaviors is the result of repeated pairing between the rewarding effects of drugs and substance-related cues (for review see Field & Cox, 2008).[17-19] The result is that substance-related cues capture and hold the attention of users (attentional bias) and elicit substance-seeking behavior.[18,19] Tobacco smokers exhibit an attention bias for smoking-related cues such as pictures, words, places or memories related to the act of smoking.[20-22] Theoretically, increases in attentional bias might be both a cause and consequence of high levels of craving. Smokers with high levels of craving are more likely to pay attention to smoking-related cues, while prolonged attentional processing of smoking related cues may increase urges to smoke. High attentional bias is associated with subjective cigarette craving [21] and risk of relapse among abstinent smokers,[23,24] and this has been confirmed among female smokers.[25,26] Thus, attentional bias plays a role in the maintenance or escalation of smoking by increasing subjective cravings and/or more directly affecting cigarette seeking behavior.[24,27,28] Attentional bias to smoking cues remains elevated in former smokers,[17-19] particularly in naturalistic settings and under conditions of stress. In a human laboratory study using the visual probe task (described below), former smokers exhibited an attentional bias intermediate between active smokers and never-smokers.[29] Animal models of relapse consistently demonstrate that drug cues and stress reinstate responding after extinction,[30-32] and cue-induced craving actually increases over 35 days of abstinence ("incubation") in abstinent smokers.[33] This is important because attentional bias predicts smoking relapse.[23-25] Therefore, manipulation of attentional bias is an important target for intervention for smoking relapse.

Assessment of Attentional Bias.

The visual probe (VP) task[34] can measure attentional bias for drug-related cues.[20,29,35,36] In the typical VP task, a pair of pictures or words (e.g. one smoking-related and one neutral) is briefly presented simultaneously side by side on a computer screen. After the pictures disappear, a probe stimulus (e.g. a small dot) is presented in the location that had been occupied by one of the pictures (or words), and participants are required to press a key as quickly as possible in response to the probe. Attentional bias for drug-related cues is detected by a faster response to a probe that replaces a drug-related stimulus (vs. a neutral stimulus), since attention will have been preferentially allocated to that area of visual display. The traditional VP task only assesses attentional bias, and does not modify it in any way.

Attentional Retraining (AR) and Addiction.

Cognitive bias modification (CBM) procedures are interventions aimed at changing the impulsive (automatic) processes that underlie unhealthy behaviors such as smoking.[37] AR is the most commonly used CBM intervention in the study of addiction-related attentional bias. The idea behind AR is to reduce attentional bias and therefore minimize exposure to drug cues, because attention to such stimuli may provoke craving and undermine cessation attempts (for review see Wiers et al., 2013).[38] A modified visual probe task has been utilized to manipulate

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attentional bias and "retrain" individuals' attention away from drug-related cues.[39-42] That is, AR administered with the modified VP task can change (and not simply assess) attentional bias. Two studies have evaluated the effects of AR to enhance abstinence and/or reduce substance use in treatment seeking individuals.[42,43] A randomized trial of AR in alcohol dependent subjects showed that AR, delivered in 5 sessions over 21 days, reduced attentional bias and relapse was delayed by over a month after the intervention. In an uncontrolled trial, drinkers with harmful alcohol use completed 4 weeks of AR and were found to exhibit a reduction in both attentional bias toward alcohol-related stimuli and alcohol consumption, an effect that was maintained 3 months after the trial.[43] AR has been used in the laboratory setting to reduce attentional bias toward smoking-related stimuli and blunt cue-provoked craving with success in some,[39,40] but not all studies.[44] Some important limitations to the evidence for AR in smoking is that all studies have included a single laboratory session among non-treatment seeking current smokers, unlike the alcohol studies that were successful after multiple sessions of AR in treatment seeking individuals. Thus, AR for smoking shows promise but some modifications are needed beyond what has been employed to date to enhance abstinence.

***AR and Anxiety*.**

AR has also shown promise for the treatment of depression and anxiety, and two meta-analyses have confirmed that AR produces significant reductions in anxiety.[45,46] Most pertinent to the current study, AR also attenuates state anxiety reactions to stressful life events.[47,48] The idea behind AR for the treatment of anxiety is to minimize the exposure to threat cues that may provoke anxiety. See et al. (2009) reported that 15 sessions of AR delivered via a home-based AR procedure reduced anxiety associated with transition stress in a naturalistic setting.[48] Postpartum women experience transitional stress, and this is associated with relapse. We posit that attending to the pathway between stress/anxiety and relapse will strengthen an AR intervention for smoking.

3. **Research Plan:** Provide an orderly scientific description of the study design and research procedures as they directly affect the subjects.

Subjects: Participants will be 50 abstinent smokers, recruited during pregnancy, who provide written informed consent. We will recruit participants at the "Women's Center" and its affiliated "Maternal Fetal Medicine High Risk" obstetrical clinics at Yale-New Haven Hospital (YNHH).

Inclusion Criteria: 1) Women with a history of smoking 5+ cigarettes per day that have achieved abstinence defined as no smoking or smoking less than 2 cigarettes per week by 32 weeks' gestation during pregnancy by 32 weeks gestation; 2) aged 18 to 40 years; 3) able to speak and write English; 4) Edinburgh Postnatal Depression Scale (EPDS) score <10.

Exclusion Criteria: 1) Current substance abuse (e.g., alcohol, benzodiazepines, marijuana); 2) current major depressive disorder, minor depression or dysthymia, or history of any of these disorders in the last 6 months; 3) presence of an Axis I psychotic disorder; 4) plans to relocate out of the area 5) imminent incarceration; 6) planned inpatient hospitalization during study period.

<u>Study Procedures</u>

Overview: We propose to randomize 50 abstinent pregnant smokers to receive either the attentional retraining (AR) or control VP task. Participants will be asked to carry around a smartphone as they go about their daily lives for 2 weeks in their last month of pregnancy (Phase 1). The smartphone will sound an alert randomly during the day, at which time participants will be asked to respond to a short set of questions assessing subjective states; this will be followed by a request to complete the AR (or control) procedures. This same procedure will be repeated for 2 weeks immediately after delivery (Phase 2). Women will undergo a follow-

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up visit 3 months after the end of Phase 2, and complete an unmodified VP and follow-up assessments. Given the COVID-19 pandemic screening will be done by phone and study visits, with the exception of Visit 1, will be done via Zoom. If/once it is appropriate to resume in person visits, participants will be offered the option of completing study visits in person at the research clinic or via Zoom.

Screening:
We will obtain referrals from providers in the reproductive health clinics at Yale New Haven Hospital and via the YCCI. Women referred from the prenatal clinics will receive an information sheet by their obstetrical provider during a routine prenatal visit that describes the study. Women will provide verbal consent if they are interested in being contacted by a study staff, and the obstetrical provider will provide their name and contact information to study staff.

Referred women will be contacted by phone by a research assistant who will administer a screening survey to determine provisional eligibility after providing verbal screening consent. In the future, when in person screening is appropriate, we will also have a research assistant approach pregnant women in the reproductive health clinics at Yale New Haven Hospital. while awaiting a routine visit will be invited to complete the screening survey to determine provisional eligibility after providing verbal screening consent. We will invite and consent provisionally eligible women to partake in the study. If screening is done by phone women will be provided a link for the online consent form via email. Women who are not eligible will be given the number for the CT “QUIT” line and educational material (Forever Free for Baby and Me ™).[49]

At the time of recruitment women will be screened using the following instruments: the PhenX Toolkit measures described below, the Fagerstrom Test for Nicotine Dependence (FTND), to obtain a quantitative measure of the severity of nicotine dependence.[50] A self-report cigarette smoking history, including timeline follow-back (TLFB) for the past one week,[51,52] the Minnesota Nicotine Withdrawal Scale (M-NWS),[53] and the Brief Questionnaire on Smoking Urges (QSU-brief)[54] will also be administered at enrollment. These assessments will be done via an online survey, a link for which will be provided by email if done by phone or a study laptop if done in person

Based on their level of smoking women will be stratified into moderate use (5-19 cigarettes/day) or high use (>20 cigarettes/day). Given the sample size we will not be controlling for breastfeeding. However, based on our experience with this population approximately half of women choose to breastfeed.

Enrollment: We will follow eligible women that have not reached 32 weeks gestation at the time of screening and determine if they are still eligible for randomization. For women who are eligible for randomization we will perform an intake interview via Zoom (Visit 1, part a) that will include a review of study procedures and consent, and computer administered intake assessments (Table 1, Visit 1). Research staff will then coordinate to meet the participant before or after a routine prenatal visit to be provided with the study smartphone and home breath carbon monoxide monitor (Visit 1, part b). They will undergo a brief training on the use of the study program (including a baseline VP task) and the CO monitor on the smartphone. They will also be asked to provide a breath sample for carbon monoxide analysis. This entire in person visit will last 15 minutes. In the future, parts a and b of Visit 1 can be done as one once it is appropriate to conduct routine study visits in person.

At this point participants will be randomized to one of the two study conditions: attentional retraining (AR) or control. All enrolled women will be provided with educational materials to help them maintain abstinence from smoking.

Urn Randomization: Eligible women will be assigned to the two study conditions through “urn” randomization to ensure relatively equal allocation between treatment group (AR) and control

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with respect to age and severity of nicotine dependence. In urn randomization, an algorithm modifies ongoing randomization probabilities based on the prior composition of treatment groups,[55] thus the allocation sequence is not pre-specified so allocation concealment is not necessary (see Sofuoglu et al. 2007).[56] To distribute age evenly over the two groups, a categorical variable will be created, 1= ages 18 to 30 and 2 for >30, because older women are more likely to achieve abstinence.[1] To explicitly require balance between groups with respect to level of dependence, a categorical variable will be created based on the number of cigarettes/day in the month before conception: 1=1-10; and 2=11 or more cigarettes on average, per day. Lastly, we will balance groups with respect to women with and without an anxiety disorder. Both the participant and the research assistant will be blinded as to the condition. Both the participant and the research assistant will be blinded as to the condition assignment.

Intervention Phase 1- Pregnancy: Following enrollment and randomization women will be asked to carry a smartphone as they go about their daily lives and complete 2 random assessments per day and an AB assessment every day for 2 weeks. Random assessments are comprised of questions assessing subjective states (see section d) and the AR (or control) procedure (described below). Data from each of the random assessments and AB assessments are transmitted in real-time allowing compliance to be assessed. If a participant responds to less than 2 random assessments on any study day a research assistant will contact the participant to encourage them to maintain compliance. At the end of the two weeks women will complete Visit 2 via Zoom and complete a post-training unmodified VP task and the Visit 2 assessments outlined in Table 1 and described below. If/once it is appropriate to resume in person visits, participants will be given the option of completing this visit in person at the research clinic.

All EMA procedures and VP tasks will be conducted on a smartphone running an application programmed by Terminal C, a Houston-based company.

Intervention Phase 2- Postpartum: Within 4 days of delivery, women will complete another VP task) and the Visit 3 assessments (Table 1). Participants will be asked to repeat the same procedure as in Phase 1, 2 random assessments per day and an AB assessment every day for 2 weeks. Once again at the end of 2 weeks they will schedule a visit via Zoom and complete an unmodified VP task and Visit 4 assessments. If/once it is appropriate to resume in person visits, participants will be given the option of completing this visit in person at the research clinic.

Post-treatment Visit: Follow-up visits, 5 and 6, will be scheduled 3 and 6 months, respectively, after phase 2. Women will complete an unmodified VP task and the assessments listed in Table 1. Again visits will be done via Zoom; if/once it is appropriate to resume in person visits, participants will be offered the option of completing these visits in person at the research clinic.

Assessments: A summary of the timing of assessments is shown in Table 1.

a) Screening and Enrollment Assessments: **The study screening form** will collect personal contact information and significant other contact information. This will be kept in a file that is separate from study assessments. In this way, sensitive data cannot be linked with participant information that could lead to a breach of confidentiality. The following PhenX Toolkit measures will be used at enrollment: General Psychiatric Assessment (without the PTSD and anxiety subsections), Substance Abuse and Dependence measure for alcohol, drugs and tobacco, and the Tobacco Protocols. The General Anxiety Disorder-7 (GAD-7) and PTSD Checklist for DSM-5 (PCL-5), validated tools to assess for anxiety and PTSD, respectively. **Fagerstrom Test for Nicotine Dependence (FTND)** consists of six items that give a quantitative measure of the severity of nicotine dependence.[57] The Penn State Electronic Cigarette Dependence Index (PSECDI), will be used to assess electronic cigarette use using a standardized validated tool.[80] The FTND is closely related to biochemical indices (e.g., CO levels, plasma cotinine) of tobacco smoking. The **Edinburgh Postnatal Depression Scale**

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(EPDS) will measure depressive symptoms.[58,59] It is designed specifically for use with pregnant and postpartum women. The scale is 10 items, internally consistent (Cronbach's □ = 0.87) and has been used in multiple different languages and different cultures. The **Modified Kendler Social Support Interview (MKSSI)**[60,61] is a 21 item scale that measures social support from family and friends. We modified it and determined its psychometric properties in perinatal women.[61] Principal components analyses found that there is a single dominant factor. We will use the 19-item self-rated **Pittsburgh Sleep Quality Index (PSQI)**,[62] to measure sleep quality; a cut-off of 5 has 90% sensitivity and 87% specificity to discriminate between "good"/"poor" sleepers, and has been used in postpartum women [63] (visits 2-5). Breath carbon monoxide will also be measured.

b) Smoking cessation outcomes (Visits 1-6): **Expired breath carbon monoxide (CO)** level will be determined with CoVita piCO+ Smokerlyzer device if a visit is done in person or with Covita iCO™ Smokerlyzer® monitors for remote visits. The iCO monitors simply plug into a smartphone. During remote visits participants will be required to breathe into the CO monitor in front of a member of the research team. Participants can email or call the project staff if they experience any difficulties with the CO monitor. Breath CO levels are only sensitive to recent smoking because of its short half-life (2 to 3hours). For smoking abstinence, a CO level of < 8 ppm will be used.[64] **Self-report cigarette smoking history** including timeline follow-back (TLFB) for the past one week. **Minnesota Nicotine Withdrawal Scale (M-NWS)** assesses DSM-IV symptoms of tobacco withdrawal such as craving for nicotine, irritability, anxiety, difficulty concentrating, restlessness, headaches, fatigue, increased appetite, weight gain and insomnia.[53] Subjects are asked to rate the presence of symptoms on a scale from "0" (not present) to "3" (severe). **Brief Questionnaire on Smoking Urges (QSU-brief)** is a 10-item scale originally developed by Tiffany and Drobes.[54] This scale has been found to be highly reliable and reflects levels of nicotine deprivation.[67,68] Similar to NWSC, this scale will be used to monitor abstinence- and cue-induced cigarette craving. This scale will be used to monitor response to treatment. Smoking intention questions will be asked at screening, Visit 1 (enrollment).

c) **Stress and anxiety outcomes** (Visits 1-6): The Perceived Stress Scale (PSS) will be used to assess stress at study visits and the short form (4-items) on the final daily smartphone assessment (see Table 2). The PSS has high reliability in a smoking cessation sample (Cronbach's α=.86).[69] The state scale of the Spielberger State-Trait Anxiety Inventory (STAI-S)[70] (Cronbach's α=.89)[71] will be used to assess the impact of the transition stressor, arrival of new baby, on anxious mood state and to determine whether this is affected by AR. The Parenting Stress Index (PSI)-Short Form,[72] an established measure of parent and child behaviors, can assess a wide range of parenting behaviors with good reliability (Cronbach's α=.83). To assess for race-related stress among African American participants we will use the Index of Race-Related Stress–Brief Version (IRRS-B), a 22- item measure of race-related stress on cultural (Cronbach's α=.78), institutional (Cronbach's α=.69), and individual (Cronbach's α=.78) racism.[73] Based on feedback from participants we have added a sentence to the introduction of the IRRS-B that acknowledges some of the language used in this questionnaire may be considered "dated" by some individuals and may not reflect current preferences for racial identity. To assess for cultural stress among Hispanic women we will use the Hispanic Stress Inventory-2 (HSI2), which has both an immigrant (Cronbach's α = .97) and US-born version (Cronbach's α = .93).[74] Social support as a measure of stress will be assessed on the final daily smartphone assessment via an adapted form of the 6-item version of the Social Support Questionnaire.[76]

d) **Smartphone Assessments:** Participants respond to the following items on 7-point Likert-type scales (1 = Strongly Disagree, 7 = Strongly Agree) according to how they feel "right now": **1)** Craving - A single item is used to assess craving for cigarettes; **2)** Difficulty concentrating - A single item will be administered to evaluate difficulty concentrating, used in previous EMA studies;[75] **3)** Affect - Items include: enthusiastic, happy, relaxed, bored, sad, anxious, angry. Two additional items assess overall mood

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and energy/arousal levels; **4)** Parenting stress – 2 items adapted from the Parenting Stress Index[72] (can't handle things, trapped by parenting) will be administered; **5)** Self-reported attention capture - 3 items will be used to assess the subjective sense to which the participant feels that their attention has been captured by smoking stimuli (e.g., "Since the last assessment, how often have you found yourself staring at cigarettes and cigarette smoke?"); **6)** Environment - 3 items assess testing and lighting conditions (e.g., whether they are currently indoors or outdoors); 2 items assess context (whether participants are alone or with others, and whether they are at home/work/ in transit/at a bar or restaurant/somewhere else); **7)** Lapses - 2 items assess the recency of the last cigarette smoked; **8)** 2 items to assess the degree of alcohol/coffee drunk in the past two hours.

e) **COVID-19**: We will assess the impacts of the COVID-19 pandemic. This will help determine the impact of COVID-19 on participants and their anxiety or smoking behavior. This questions have participants rate questions on a scale (1= not at all, 5 = to a great degree) access affect ("To what extent has coronavirus affected your income?"), supplies ("To what extent has conronavirus affected your ability to get food and supplies to take care of your family and household?"), support ("To what extent has coronavirus affected the level of support you normally receive from family, friends, and your community?") , healthcare ("To what extent has coronavirus affected your ability to get the healthcare you need for yourself and/or your baby?"), depression ("To' what extent has coronavirus increased your feelings of depression?"), anxiety ("To what extent has corona virus made you more anxious?"), and impact ('I frequently spend time thinking about coronavirus and its impact on my life?").

Table 1: Study Assessments

		Phase 1 - Pregnancy		Phase 2 - Postpartum		Post-treatment	
Measure	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Timing	≤32 wks gestation	Enrollment, 32 wks	End of Phase 1	Start of Phase 2	End of Phase 2	3 months	6 months
Screening form	x						
Smoking history	x						
PhenX Toolkit	x						
FTND	x						
MKSSI		x					
GAD-7 and PCL-5	x						
TLFB	x	x	x	x	x	x	x
Breath CO		x	x	x	x	x	x
EPDS	x	x	x	x	x	x	x
PSQI		x	x	x	x	x	x
PSI				x	x	x	x
IRRS-B/HSI2		x	x	x	x	x	x
PSS		x	x	x	x	x	x
STAI-S		x	x	x	x	x	x
MNWS	x	x	x	x	x	x	x
QSU-brief	x	x	x	x	x	x	x
Feeding intention		x		x			
H&H lactation					x	x	x
Infant feeding					x	x	x
E-cig questions	x	x	x	x	x	x	x
Standard VP task		x	x	x	x	x	x
Motivation to stop smoking	x	x			x		
COVID-19		x		x		x	x

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Smartphones: All EMA procedures will be conducted on Apple iPhones. Application programming will be done by Terminal C, a Houston-based company. Participants need not possess any computer skills or know how to type. In addition, participants will be locked out of

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all functions other than our program. Thus, other programs cannot confuse them. The main smartphone functions will be disabled (e.g. they will not have voice or text capabilities) and therefore are essentially worthless for anything but delivering the study application. Because of its small size (i.e., roughly equivalent in size to a pack of cigarettes), the smartphone is easy to carry in a pocket or purse. Learning to use the smartphone is very simple and does not require previous computer experience. Participants can email or call the project staff if they experience any difficulties with the smartphone.

AR Intervention: Women randomized to AR will be scheduled to complete 2 AR tasks per day. On the AR tasks, the dot always replaces the neutral picture (or word). There is a perfect correlation between picture type and dot location. Consistent with prior work each AR task will target both the initial orienting of attention (40 trials x 200 ms picture presentation) and the disengagement of attention (40 trials x 500 ms picture presentation).[42] Based on pilot data, the mean duration of AR (and control) assessments is expected to be about 5-7 minutes. There will be 2 types of AR interventions, one targeting smoking-related stimuli and one targeting stress. The type of AR (smoking vs. stress) will alternate daily between the 2 AR tasks. For the smoking AR intervention we plan to use 15 picture sets of consisting of 20 culturally appropriate picture pairs (one smoking-related and one neutral) each. One picture set will be administered on each study day (days 0-14 in pregnancy and days 0-14 postpartum). For the stress AR intervention we plan to use 15 culturally appropriate word sets with 20 word pairs each. Word pairs consist of one emotionally neutral rated word (e.g. book) and an emotionally negative rated word (e.g. fear). We base this on the work of See et al., who demonstrated that AR was effective in inducing attentional avoidance of negative/stressful information (words), thus reducing anxiety related to a naturalistic stressor.[48] Again one word set will be administered on each study day (days 0-14 in pregnancy/postpartum). To facilitate compliance, a “delay” option will allow women to delay their response by 5 minutes, a “suspend” option will prevent the phone from presenting assessments for a specific time period, and a “make-up” option will allow women to complete trainings if they miss an AR or have technical difficulties (e.g. program crashes and prevents random assessment from being presented). The program is operational independent of internet connectivity, as it will run directly on the smartphone. Data will be stored on the phone and wirelessly backed-up on a server.

Control Condition: The control task is identical to the AR task in number of tasks per day, number of trials per task (80 trials: 40 x 200ms and 40 x 500ms picture presentation) and the types of tasks: one containing smoking-related and neutral pictures (smoking control task), and one with stress-related and neutral words (stress control task). The only difference is that in the control task, the dot is equally likely to replace the smoking picture (or stress-related word) and the neutral picture (or word). There is a zero correlation between picture type and dot location, therefore there is no effect on AB. This type of control condition has been used in previous AR studies[77] and in our own pilot study, and ensures that: 1) the duration of AR and control training should not differ; 2) AR and control participants receive equal practice on the motoric aspects of the VP tasks; and 3) AR and control participants are exposed to the same smoking and neutral pictures or stress-related and neutral words. Note that, apart from the number of trials, the control task is the same as the standard VP task.

Attentional Bias Assessment: We will assess attentional bias using the standard VP task on the final random assessment of each day. Consistent with the AR task and prior work,[42] the VP task will have stimulus presentation durations of 200 ms and 500 ms at each assessment. This will allow us to assess both the initial orienting of attention (20 trials x 200 ms) as well as the difficulty disengaging attention (20 trials x 500 ms), for a total of 40 trials.[17] It will include a balance of both smoking and stress cues. Processing of reaction time data and computation of attentional bias will follow existing procedures.[22,78] Reaction times (RTs) will be computed from trials with correct responses. We will compute attentional bias scores as the difference in RTs on trials where the probe replaced the smoking picture (or stress-related word) vs. trials where the probe replaced the neutral picture (or neutral word). Faster RTs on the former reflects an attentional bias towards to the smoking picture/stress-related word, or vigilance. Faster RTs on

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the latter reflects an attentional bias away from the smoking picture/stress-related word, or avoidance.

4. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data Analysis: Given the small sample size and the goal of feasibility, we will plot the potential mediator/moderator covariates and relapse over time. These data will be exploratory only but will provide a rough assessment of the process of relapse (Hypothesis #1) in relation to a number of covariates. We will use Generalized Estimating Equations (GEE)[79] to evaluate the relationship between the "sad" mood measure and risk of relapse to smoking. For Hypothesis 3 and 4, assuming normal distribution of attentional bias toward smoking and stress cues we will utilize a linear mixed model (LMM) to compare change in the intervention group to change in the control group (see Table 2). Mixed models allow for missing observations and within subject clustering. The best fitting correlation structure will be selected based on Schwartz-Bayesian criterion. We will use all available data in an intention-to-treat analysis. Assessment number and assessment number-group interaction will be included in the model as fixed effects. The overall difference in slopes between the two groups will be tested. Presentation duration, a categorical variable with two levels (200 ms vs. 500 ms), will also be included as a fixed effect. If data are not normally distributed, we will attempt transformation to normality. If data are skewed and complied at zero, we will use a generalized linear mixed model and approximate data by a Poisson distribution, a Zero-Inflated Poisson distribution (ZIP) or a negative binomial distribution. If parametric models are not appropriate, we will use a nonparametric approach for repeated measures. Attentional bias outcomes assessed in the lab will also be examined using LMMs. Analysis for cravings and stress will be similar except that presentation duration factor will not be included; for craving, an additional categorical variable, number of assessment within the day, will be included. We realize that there will be limited power for this statistical analysis but we will be able to detect large effects.

Table 2: Data Analysis Variables

Variable Type	**Independent**	**Dependent**			
Variable	AR vs. Control	Attentional Bias to Smoking Cues	Attentional Bias to Stress Cues	Craving	Stress
Intervention	Modified VP*	(n/a)	(n/a)	(n/a)	(n/a)
Assessment	(n/a)	VP*	VP*	1-7 scale; cue-provoked	PSS
Modality	Smartphone	Smartphone	Smartphone	Smartphone	Smartphone
Frequency	2	1	1	3	1
Hypothesis		**Hypothesis 3a**	**Hypothesis 4a**	**Hypothesis 3b**	**Hypothesis 4b**

Note: VP = visual probe; *200 + 500 ms presentation; Frequency = number of tasks/assessments per day

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SECTION VI: RESEARCH INVOLVING DRUGS, DEVICES, BIOLOGICS & PLACEBOS

Are there any investigational devices used or investigational procedures performed in a YNHH Operating Room? Yes ☐ No ☒ *If Yes, please be aware of the following requirements*:

1. **Identification of Drug, Device or Biologic:** What is (are) the **name(s)** of the drug(s), device(s) or biologic(s) being used? Identify whether FDA approval has been granted and for what indication(s).

All protocols which utilize a drug, device or biologic **not** approved by, but regulated by, the FDA must provide the following information: ☒ **Not applicable to this research project**

SECTION VII: HUMAN SUBJECTS

1. **Recruitment Procedures:** Describe how potential subjects will be identified, contacted and recruited.

We will obtain referrals from providers in the reproductive health clinics at Yale New Haven Hospital and via the YCCI. YCCI has an ever growing "Help us Discover" database of approximately 8,000 valid email addresses of individuals who have volunteered to be contacted about clinical research at Yale. The emails go out periodically to the database and study teams have found that interest and recruitment for their clinical trial has greatly increased after an email campaign.

Referred women will be contacted by phone by a research assistant who will administer a screening survey to determine provisional eligibility after providing verbal screening consent. In the future, when in person screening is appropriate, pregnant women awaiting a routine visit in the reproductive health clinics at Yale New Haven Hospital will be approached by a research assistant and invited to complete a screening survey to determine provisional eligibility after providing screening consent. We will invite and consent provisionally eligible women to partake in the study. After screening, women who are not eligible will still be offered referrals.

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

☒ Flyers (in OB/Gyn clinic)	☒ 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	

☒ Other (describe): YCCI "Help us Discover" database and Joint Data Analytics Team (JDAT) reports of eligible participants

☐ Clinicaltrials.gov Registry (do not send materials to HIC)

2. **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

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☐ Yes, some of the subjects
☒ No
If yes, describe the nature of this relationship.

2. **Subject Population** Provide a detailed description of the targeted involvement of human subjects for this research project.

   All participants will be women, as only women can become pregnant. Participants must be age 18 or above, with a recent problem of nicotine dependence. Previous work with this population in this same clinic yielded a subject sample averaging 25.5 years old, 3.3 previous pregnancies and 1.2 other children in the home. We anticipate the following racial/ethnic breakdown in our sample, based upon previous work with the same population in the same clinic: 47% African American, 30% Caucasian, 23% Hispanic. Given the use of specialized smartphone program we have determined to offer the study only to English-speaking patients, and do not believe this will limit recruitment nor access to care for patients in need.

3. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion? How will eligibility be determined, and by whom?

   Inclusion Criteria: 1) Women with a history of smoking 5+ cigarettes per day that have achieved abstinence during pregnancy, with abstinence defined as no smoking or smoking less than 2 cigarettes per week by 32 weeks' gestation; 2) aged 18 to 40 years; 3) able to speak and write English; 4) Edinburgh Postnatal Depression Scale (EPDS) score <10; 5) have biologically confirmed abstinence from tobacco and other nicotine products at randomization.

   Exclusion Criteria: 1) Current substance use, with the exception of cannabis, if not used in a combustible form (e.g. edibles, teas, tinctures, etc.); 2) current major depressive disorder, minor depression or dysthymia, or history of any of these disorders in the last 6 months; 3) presence of an Axis I psychotic disorder; 4) plans to relocate out of the area 5) imminent incarceration; 6) planned inpatient hospitalization during study period.

   The PI or research staff will screen potential subjects using the assessments described under study procedures. This includes modules from Addiction Severity Index, the Edinburgh Postnatal Depression Scale, the PhenX Toolkit measures (see Table 1). At intake, postpartum, subjects will complete the Kendler Social Support Inventory, Parenting Stress Index and a Substance Use Calendar. In addition, they will undergo an expired CO breath test to confirm smoking abstinence, at the time of enrollment (Visit 1, see Table 1 above). After assessments the PI will confirm whether or not the respondents met criteria outlined above.

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

   4.b. If yes, will identifiable health information be collected during this screening process and retained by the research team? ☐ xYes☐ No

5. **Subject Classifications: Check off all classifications of subjects that will be invited to enroll 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
☐ Decisionally Impaired	☐ Employees	☒ Pregnant women and/or fetuses
	☐ Students	☐ Females of childbearing potential

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5.a. 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)

SECTION VIII: CONSENT/ ASSENT PROCEDURES

1. **Consent Personnel:** Please see IRES-IRB.

2. **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.

   All potential participants are asked to provide written informed consent for study participation. Study visits, including intake, are scheduled as independent visits and are held at our research office where meeting spaces are private and confidential. Participants will be told that they are not protected against mandatory reporting of child abuse, suicidality or homicidality.

3. **Evaluation 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.

   All patients will be required to be competent to sign written informed consent. Capacity to consent will be assessed in a systematic format. Any subject that is interviewed and appears to have limited decision-making capacity will undergo further evaluation of capacity to consent. Ultimately, the PI will determine the capacity to consent in any case where it may be in doubt. Cases will be treated on a case-by-case basis with the PI making the final decision on cases of questionable capacity to consent. Patients that are determined by the PI to not possess the capacity to provide consent will be provided with information on smoking and a referral list for agencies and treatment providers.

4. **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.

   Women referred from the prenatal clinics will receive an information sheet by their obstetrical provider during a routine prenatal visit that describes the study. Women will provide verbal consent if they are interested in being contacted by a study staff, and the obstetrical provider will provide their name and contact information to study staff. Referred women will be contacted by phone by a research assistant who will administer a screening survey to determine provisional eligibility after providing verbal screening consent. At this point if women are preliminarily eligible they will be invited to participate in the study and undergo formal (signed) informed consent as outlined below. Women who are not provisionally eligible will be thanked for their participation in the screening process and given a $20 Amazon e-gift card.

   The procedure for obtaining informed consent entails a face-to-face or Zoom discussion between the potential subject and a trained member of the research staff. The entire protocol and all of its requirements are explained at length. Additionally, women are encouraged to ask questions about any confusing points. Subjects are told that they may withdraw from the project at any time, without prejudice, and without any adverse effect on their medical care at their prenatal clinic.

5. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must

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be submitted for approval prior to use.

Not applicable to this study.

6. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:

Waiver of consent: (No consent form from subjects will be obtained.)

a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ xNo
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ xNo
c. Why would the research be impracticable to conduct without the waiver?
   - Without the waiver, we would be unable to identify patients who may be eligible through the electronic health record (EHR). Given the limitations for in-person presence at clinical sites due to the COVID-19 pandemic, we rely primarily on identifying potentially eligible participants via EHR. Without this we would be unable to meet our recruitment and target enrollment. It is not feasible to obtain consent a prior for the EHR searches conducted by JDAT. We will not be collecting any data from the searches other than name and phone number of potentially eligible subjects. If we identify potentially eligible subjects, they will be asked for full consent before deciding to participate in the study.
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? N/A

Waiver of **signed** consent: (Verbal consent from subjects will be obtained.) For screening only. Women will be given an information sheet by their obstetrical provider briefly describing the study and the screening process for which they will provide verbal consent to be contacted.

This section is not applicable to this research project

a. Would the signed consent form be the only record linking the subject and the research? ☐ xYes☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ xYes☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ☐ No **AND**
d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

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. 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/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

It is not feasible to obtain consent a prior for the EHR searches conducted by JDAT. We are unable to know ahead of time which patients might meet eligibility criteria and therefore have no way of obtaining consent. The waiver of HIPPA authorization allows us to identify patients who are potentially eligible via the EHR searches conducted by JDAT. We would utilize the name and phone number of potential participants to complete phone screenings. Again, since this information is collected via EHR searches we are unable to obtain consent to call participants ahead of time. At the time of the phone screening, we will obtain verbal consent to conduct the screening call, and they will be asked for full signed consent before deciding to participate in the study. As noted elsewhere in the protocol, we have procedures in place that allow us to obtain signed consent remotely.

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.

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

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

Questionnaires and interviews will contain items of a personal nature. It is possible that the process of psychiatric interview may feel uncomfortable for some respondents. It is unlikely that completion of the questionnaires will lead to any legal, social, or psychological problems. Another potential risk is the loss of privacy. There are no known risks associated with the subjective assessments related to the smartphone assessments. There are no data to suggest that the attentional retraining or control task promotes smoking, although this will be monitored carefully. The use of the CoVita iCO+ Smokerlyzer device, per se, do not pose risk to the subject. There is no reason to believe that participants' smoking will be increased by participation in the study.

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

Any potential discomfort with the completion of the screening questionnaire and psychiatric interview will be minimized by appropriately preparing the patient for the computerized assessment by the PI or research staff trained to deal with such difficulties and explaining the study, consenting, and screening women in private.

Loss of privacy is minimized with the self-administered assessments since only the subject completing the interview can read the interview questions and responses. These assessments will be identified by the subject ID number only, maintaining the anonymity of the responses. Other data collected for this protocol will be kept in a research chart and this information will only be available to research staff unless the imminent safety of the participant or her dependents is at risk (see below). Smokers will have the option of declining to answer any questions that they find objectionable, or of withdrawing from the study at any time.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan

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(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? The study does not involve investigational drugs. The risks to the participants are low.

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. Data and Safety Monitoring Plan
For Data and Safety Monitoring Plan templates, see
http://www.yale.edu/hrpp/forms-templates/biomedical.html

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, quarterly. 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 Human Investigation Committee (HIC) 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, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 5 days to the HIC (using the appropriate HIC 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 or via email as they are reviewed by the principal investigator. The Clinical Supervisor will review subjects' safety daily and will present subjects' clinical status and adverse experiences in the weekly Study Personnel meeting. Entrance criteria of all subjects are reviewed at this meeting including results of screening assessments. The referral to appropriate care for subjects who endorse clinical deterioration will be monitored at this meeting. The PI will oversee appropriate assessment and referral for these subjects, and ensure that information on subjects' adverse effects are systematically collected and evaluated.

d. For multi-site studies for which the Yale PI serves as the lead investigator:

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?

4. Confidentiality & Security of Data:

a. What protected health information about subjects will be collected and used for the research?

Subjects who provide written consent will be asked for the following PHI: Name, Date of Birth, Anticipated (or actual) Date of Delivery, home address and telephone number.

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

Data will be collected on Qualtrics and saved onto a secure database saved on a secure server, managed by our Programmer and, more broadly, by the YUSM ITS department.

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Any paper files will be locked in a secure file cabinet in a locked office. Computer files are accessible by password only, and backups are secured by ITS. Computerized data will be identified by subject number only. The data from the smartphone assessments will be downloaded to the study computer, which is password protected and secured by ITS. Once a subject has completed the study and the smartphone data has been downloaded, the smartphone memory will be erased.

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

d. 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 the subject participation in the study?

All data will be coded by subject number only and will be locked in research offices. Demographic information, subject lists and progress through the study will be entered on the PI's computer which is kept at all times in the locked research clinic office. Access to the computer is password-protected. The original clinic screening data will be kept in locked file cabinets in the locked research clinic office, identifiable by subject codes only.

The smartphones themselves will be locked out of all functions other than our program to avoid confusion or unintended use of the phones. To ensure confidentiality the smartphone data collected from each subject will also be coded by subject number only. Patient identities will not be directly linked to the smartphone data. In addition, there will be no patient identifiers on the smartphones themselves. The smartphones will not store any assessment data, as data are wirelessly transmitted to a secure server (after each assessment) where they can be retrieved by the investigator. All data are de-identified and encrypted. Therefore, if the subjects lose the smartphone or someone else gains access to it there will be no compromise of personal information.

Data will be kept confidential and will not be released to the general public. Data will be available to research staff, the local IRB and government agencies as required. No subjects will be identified by name in any report of the study.

e. What mechanisms are in place to ensure the proper use and continued protection of these data after the subject participation in the study has ceased?

After study completion, data may be provided to other researchers after a written request and after any possible identifying information is purged. All disclosure rules pertaining to HIPAA will be followed in the exchange of any study data with other researchers.

f. 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.

Upon completion of data analysis, this data will be used to support future grant submissions. We will not destroy the data until 7 years after study completion. Security measures will be the same as noted above.

g. Who will have access to the protected health information? (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, QUACS, SSC, etc.)

PHI will be accessible to the PI, Research Staff, and the HRPP.

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h. Which external or internal individuals or agencies (such as the study sponsor, FDA, QUACS, SSC, etc.) will have access to the study data? HRPP

i. If appropriate, has a Certificate of Confidentiality been obtained? N/A

j Are there any mandatory reporting requirements? (Incidents of child abuse, elderly abuse, communicable diseases, etc.)
In the unlikely event that we learn of risk of neglect or abuse of a child, we will report this to the State of CT DCF Hotline.

5. **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.)

Postpartum smoking may lead to continued smoking into the next pregnancy with associated harm to the fetus and the newborn. Perhaps equally harmful are the health effects of second-hand smoke on newborns. Women who smoked pre-pregnancy have less intent to breastfeed or cease breastfeeding early in order to restart smoking. Women participating in this study will be provided with a referral to the CT Quit Line if they relapse. Some participants may reduce their smoking over the course of the week. Some participants may experience reduced cravings. More broadly, data from the study may help us develop better smoking cessation programs. This may be beneficial to smokers and to society. Finally, knowledge gained from this study might be beneficial for these future endeavors.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

Treatment alternatives include referral to CT Quite Line, case management, and outpatient treatment according to the centers' usual protocol. Subjects may still receive case management (e.g. assistance with community resources and/or peer support) from clinic staff, without participating in this protocol. Participants will be provided with information regarding smoking while pregnant and smoking cessation resources by the research assistant during each visit, if necessary. The PARIS study website and introduction packet provides resources for treating tobacco use disorder including Smokefree women, CDC and the CT commit to Quit line.

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.

Subjects will be compensated as much as $400 for completing the entire study, stratified by visit type and assessment completion and will be as follows:

They will be paid $20 for completion of the initial screening assessment. During the study they will receive $2 for each smartphone assessment they complete, plus $8 per week for completing all assessments for the week (up to $200 for completing all 84 assessments); $20 for each study visit (Visits 1-4); and $50 for each follow-up visit (Visit 5 and 6). Compensation for the assessments completed in Phase 1 will be provided during Visit 2, and compensation for the assessments completed in Phase 2 will be provided during Visit 4. The compensation may enhance compliance with all assessments. Compensation will be via Amazon e-gift card, which participants will receive after completing a study visit via a link by text or email.

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Participants will be gifted the smartphones as part of their participation in the study once visit 4 is complete. Once they have completed all both phases of the study the phone will be unlocked to all other functions, which are restricted during the study period. Participants who complete phases 1 and/or 2, they will be asked to complete a short feedback survey which they will be paid $10 for completion.

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. None

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   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?

   This study does not entail physical procedures that may cause injury. No compensation is available for emotional injury or injury to offspring. All patients enrolled in study are currently receiving health care at the study-sponsoring obstetrical clinic.

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APPENDIX

Visual Probe (VP) task

The following is a description of the visual probe task used by Waters et al. (2003). We will be following this protocol in our study. The stimuli consisted of color photographs of smoking-related scenes (e.g., woman holding a cigarette to mouth). Each was paired with a control photograph of another scene lacking any smoking-related cues (e.g., woman applying lipstick). Thus, the smoking and control pictures were similar on visual characteristics. The pictures were each 500x500 pixels when displayed on the screen.

The task consisted of 160 experimental, which were presented in a new random order for each subject. At the start of each trial, a fixation cross was displayed in the center of the screen for 500 ms. There was an interstimulus interval of approximately 250 ms between the fixation cross offset and picture onset (allowing transfer of picture files from hard disc to video memory). The picture pair was then presented for 500 ms, one picture each side of the central position. The dot probe was displayed immediately after the offset of the pictures, until subjects made a response. Participants were told to press one of two keys as quickly and as accurately as possible to indicate whether the probe occurred on the left or the right. On the experimental trials, each picture pair was presented 4 times. The task took around 10 minutes to complete.

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The Visual Probe Assessment Task. At the outset of each trial, a fixation cross is presented for 500 ms. No response is required or permitted.

The Visual Probe Assessment Task. Following a 250 ms delay, two stimuli are presented to the left and right of the computer screen for 500 ms. One stimulus is a smoking stimulus and the other is a neutral stimulus. No response is required or permitted during the presentation of the pictures.

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The Visual Probe Assessment Task. After the pictures disappear, a visual probe (in this case, a dot) replaces either the smoking stimulus or the neutral stimulus. The participant is required to indicate the position of the visual probe (left or right) as quickly and accurately as possible.
For the visual probe assessment task the probe is equally likely to replace the smoking and the neutral stimulus. In the above trial, the probe replaced the smoking stimulus.

The Visual Probe Assessment Task. There is a blank screen of 500 ms before the next trial. No response is required or permitted.

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The Visual Probe Retraining Task. The Visual Probe Retraining Task is the same as the Visual Probe Assessment Task, except that in the retaining task the visual probe (the dot in this case) always replaces the smoking picture.

The Visual Probe Retraining Task. Following a 250 ms delay, two stimuli are presented to the left and right of the computer screen for 500 ms. One stimulus is a smoking stimulus and the other is a neutral stimulus. No response is required or permitted during the presentation of the pictures.

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For the Visual Probe Retraining Task, the probe the visual probe (the dot in this case) always replaces the neutral picture.

The Visual Probe Retraining Task. There is a blank screen of 500 ms before the next trial. No response is required or permitted.

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