Pilot Study to Evaluate a Behavioral Activation Prenatal and Postpartum

Intervention for Depressed Pregnant Smokers

Specific Aims

Primary Aims

Aim 1 (Stage IA)

Conduct qualitative group interviews with depressed pregnant smokers and depressed smokers within the first 4 months of the postpartum period, to adapt and refine the delivery of behavioral activation therapy (BA) and health and wellness education (HW) via smartphone videoconferencing, a BA and HW smartphone application (app) including supportive smoking cessation messages in the prenatal and postpartum periods. Participants will be queried on a) barriers and supports to completing treatment sessions and study assessments; b) suggestions for decreasing barriers and increasing treatment acceptability; c) usefulness of BA, HW and smoking cessation counseling treatment materials, and; d) usefulness and acceptability of the BA and HW apps.

Aim 2 (Stage IA)

Adapt BA and smoking cessation counseling manuals, BA and HW app and content, and treatment integrity rating scales for the prenatal and postpartum period

Aim 3 (Stage IA)

Pilot test the delivery, via smartphone videoconferencing, of a 10-week treatment course of BA and HW and conduct process evaluation of technical issues in the use of smartphones, barriers to participation and retention; completion of study assessments, and; adequacy of procedures for addressing psychiatric emergencies.

Aim 4 (Stage IB)

Conduct a preliminary randomized trial with depressed pregnant smokers comparing BA to HW to evaluate: 1) Effect of BA on abstinence at 4 ½ months postpartum; 2) Effect of BA on depression at 4 ½ months postpartum; 3) Feasibility of acceptance of the smartphone delivery of BA and HW, and assessment components indicated by a) retention; b) completion of prenatal and postpartum sessions; c) completion of study assessments, d) strength of therapeutic alliance from both the participant and therapist perspective; e) participant and therapist ratings on satisfaction questionnaire; 4) Feasibility of study procedures as indicated by a) percentage of sessions interrupted by technical difficulties, and; b) percentage of urine cotinine and/or anabasine tests received for biochemical verification of self-reported abstinence at 4 ½ months postpartum.

Secondary Aims

Secondary Aim 1 (Stage IB)

Evaluate change in hypothesized treatment mechanisms including positive affect, negative affect, and cognitive function in relation to treatment effects on smoking and depression.

Secondary Aim 2 (Stage IB)

Conduct qualitative interviews with women who completed and did not complete postpartum treatment to assess a) barriers to completing treatment sessions; b) usefulness of postpartum treatment; c) suggestions for decreasing barriers and improving treatment acceptability, and; d) relevant experiences unexpected by participants and researchers.

BACKGROUND

Importance of the Problem

Comorbid depression is associated with continued smoking during pregnancy and nicotine dependence Smoking and depression frequently co-occur in pregnant women, especially in women of low-income status.[1, 2] Depression is associated with continued smoking during pregnancy. In a recent large epidemiological study, depressed women were twice as likely to continue to smoke during pregnancy than nondepressed women (16.3% vs. 7.2%).[3] Using data from the 2008-2014 National Survey on Drug Use and Health, 40% of pregnant women experiencing current serious psychological distress, as assessed by the K6 screening instrument, reported current smoking compared to 11.7% of women without recent distress.

Among women with current serious psychological distress, the prevalence of current prenatal smoking had not changed between 2008 to 2014, whereas among women without distress, the prevalence of smoking significantly declined.[4] Depression in pregnant women who smoke is strongly associated with higher levels of nicotine dependence.[2, 5] These studies suggest that depression is associated with difficulty quitting in pregnant smokers and that they may require more tailored approaches to cessation treatment.

Smoking and depression during pregnancy have independent negative effects on birth and infant outcomes Independently, maternal depression and smoking during the prenatal and postnatal periods produce pernicious effects on fetal and child health, suggesting there may be additive negative effects when these factors co-occur.[6] Smoking during pregnancy is responsible for 20% or more of the incidence of low birth weight, a condition that is associated with neonatal, perinatal, and infant morbidity and mortality.[7, 8] Pregnant women who smoke are at increased risk for a number of adverse pregnancy outcomes including placental abruption, pre-term birth, stillbirth, sudden infant death syndrome, and spontaneous abortion.[9, 10] Maternal smoking during the postpartum period is associated with infants' higher risk of hospitalization for respiratory tract and other types of infections during the first 12 months of life,[11–13] slower lung growth and lung function decrements,[14, 15] increased school absence,[15] and sudden infant death syndrome.[16, 14]

Clinically significant maternal depressive symptoms during pregnancy are associated with preterm birth and low birth weight, especially among low-income women. This effect is independent of smoking, and the magnitude of risk for preterm birth posed by clinically significant antenatal depressive symptoms is comparable to the risk of smoking 10 or more cigarettes a day.[17] The presence of affective disorders and clinically significant depressive symptoms during pregnancy have been found to be associated with abnormalities in fetal activity, low Apgar scores, poor neurobehavioral functioning, neuroendocrine abnormalities in the limbic-hypothalamic-pituitary axis at birth, newborn irritability, and fetal death.[18–21] Major depressive disorder (MDD) during the prenatal period is associated with poor maternal-fetal attachment which has been shown to negatively influence psychosocial child development.[22] Postpartum maternal depression is related to increased risk of injury among infants and toddlers,[23] decreased breastfeeding duration,[24, 25] reduced weight gain during infants' first 2 years of life,[26, 27] increased infant hospitalization[28] and emergency room visits,[29] poorer parental preventive practices for child safety [30, 31] and increased risk for adjustment problems in childhood.[32]

Scientific Premise

Brief counseling with pregnant and postpartum smokers is largely ineffective or produces low abstinence rates Psychosocial smoking cessation interventions administered during the prenatal period have yielded only modest effects and low abstinence rates of 7.6% in control conditions and 13.3% in experimental conditions.[33, 34] A more recent review of all intervention types in pregnant smokers (e.g., self-help booklets, counseling) found that the pooled mean estimate of the proportion of women smoking at end of pregnancy was 87%.[35] It is important to note that the majority of studies in this review evaluated information booklets and brief counseling interventions (15 to 90 minutes). Interventions that have offered up to 8 hours of counseling and/or multiple counseling contacts have been found to be more efficacious in pregnant smokers and have produced higher abstinence rates (*18*% to 39%).[36–38] The modest abstinence outcomes that most prenatal smoking cessation interventions have produced, decline further in the postpartum period, and in most studies, prenatal differences between experimental and control conditions are no longer significant at postpartum follow-ups.[33, 39] In the review of all intervention types, the pooled mean estimate of women smoking at 6 months postpartum was 94%.[35] A number of studies have evaluated postpartum counseling

interventions designed to maintain cessation throughout pregnancy and into the postpartum period, or to prevent relapse in women who quit on their own during pregnancy. The majority of these studies have tested low intensity counseling sessions—1 to 4 brief postpartum counseling sessions delivered by nurses and trained clinical staff.[40–48] Reviews of postpartum interventions have found no evidence of statistically significant benefits for these brief interventions.[49, 50]

Evidence that an intensive depression-focused intervention is efficacious for smoking cessation in depressed pregnant smokers In a previous randomized trial,[51] we evaluated the efficacy of an intensive,10-session prenatal smoking cessation intervention that included a depression-focused treatment component (cognitive behavioral system of psychotherapy [CBASP]), compared to the time and therapist contact health and wellness education (HW) control that will be used in the proposed study. We did not target depressed women in our recruitment. However, 23.3% of women entered the trial with current MDD and 13.6% were in partial remission of a major depressive episode. The average CES-D score for the sample was above the cut-off for possible depression (18.8). We hypothesized, a priori, that women with the highest depressive symptoms would benefit to a greater extent from CBASP compared to HW. At end of treatment, both treatments produced some of the highest rates of abstinence that have been reported at end of prenatal treatment (45.3% for CBASP and 39.2% for HW). At 6 months following end of treatment, which occurred on average at 4½ months postpartum, women in the highest quartile of CES-D scores (*M* = 35.08, *SD* = 5.07) at study entry treated with CBASP were significantly more likely to be abstinent (26% versus 9%) and had significantly lower levels of depression through 6 months postpartum compared to women in the high depression group treated with HW. These findings support the premise that clinically depressed pregnant women may benefit to a greater extent from an intensive smoking cessation intervention that concurrently addresses both depression and smoking than an intervention that addresses smoking only. However, similar to other prenatal smoking cessation studies, abstinence significantly declined by 6 months postpartum, and there were no group differences at the 6-month postpartum follow-up.

Extended psychosocial interventions are recommended for pregnant women The proposed study is in line with recent recommendations to study extended treatment approaches for pregnant smokers that allow for treatment of women in the prenatal period and postpartum periods.[52, 53] Such treatments should address factors that are associated with difficulty quitting and increased risk of relapse, such as stress, and should focus on providing continued support of both abstinent, and nonabstinent women for quitting, preventing relapse, and getting back to abstinence as soon as possible following relapse.[53] The proposed study focuses on depressed pregnant smokers, a group that is likely to experience the highest severity of factors known to be associated with relapse risk including poor mental health and stress associated with the transition from birth to postpartum.

Behavioral activation is efficacious for the treatment of depression in pregnant women and shows promise as a smoking cessation intervention in smokers with elevated depressive symptoms Behavioral activation emphasizes the relationship between activity and mood. It seeks to increase engagement in rewarding and adaptive activities, decrease activities such as avoidance and withdrawal that maintain or increase risk for depression, and solve problems that limit access to reinforcers. It has been found to be comparable in efficacy to cognitive therapy (CT) and antidepressant medication (ADM) for the treatment of current MDD[54, 55] and more efficacious than either CT or ADM in more severely depressed patients.[55] Importantly, BA has been found to be more effective than treatment as usual in depressed pregnant women when delivered by trained nurses and master level behavioral health counselors in obstetric clinical settings, and was more effective in reducing anxiety symptoms and stress.[56] In addition, there is evidence for the efficacy of BA plus

standard smoking cessation counseling compared to standard smoking cessation counseling alone in smokers with elevated depressive symptoms.[57 58]

Theoretical model for targeting both depression and smoking A recently proposed theoretical model[59] posits that among smokers with comorbid depression, adverse internal states of low positive affect (PA), high negative affect (NA) and cognitive impairment function as motivational states that predict greater reinforcement value of smoking and elicit an expectation of greater reinforcement value. Explicit goal-directed instrumental knowledge of response sequences that yield reinforcement from nicotine is acquired, which drives behavior to achieve the desired smoking outcome in specific external contexts. These incentive learning processes serve to promote smoking maintenance and relapse in depressed smokers. The theoretical framework is applicable to smokers in general. However, in those with comorbid depression, these internal motivational states are especially effective in driving smoking because depressed smokers experience more intense adverse states, thus greater reinforcement; and withdrawal is more severe, further intensifying these adverse states as smoking motivators. The high reward value of smoking in these states is particularly motivating during abstinence and is conceptualized as the primary trigger for smoking maintenance and relapse. A prediction of this model is that treatment should attenuate these states and reverse positive expectancies associated with smoking to help depressed smokers achieve cessation.

We posit that BA, given evidence of its efficacy in addressing depression and anxiety symptoms, will be more effective than HW at addressing these states and thus produce higher levels of smoking abstinence. More specifically, we hypothesize that BA will address PA through treatment components that increase availability of positive reinforcement and increase reward value of potentially pleasant events; NA through treatment components that encourage approach behavior in the context of adverse emotional states and encourage a problem-solving stance;[60, 61] and cognitive deficits resulting from BA's greater resolution of depressive symptom severity.[59] We will evaluate PA, NA and cognitive function as mediators of both smoking and depression treatment outcomes.

Smartphone videoconferencing interventions have potential reach and impact in low-income populations with psychiatric disorders Historically intensive treatment approaches have been labor intensive, cost prohibitive and unfeasible for populations such as pregnant and postpartum women. However, recent developments in mobile/internet based software provide opportunities to deliver psychotherapeutic interventions via videoconferencing.[62–66] A chief benefit of videoconferencing delivery of mental health interventions is the capability of this technology to display visual and auditory information, which offers a greater proxy to traditional in-person service delivery than web- or telephone-based treatment delivery and may be especially important when delivering more complex, empirically-validated interventions. Delivery of empirically-validated psychotherapies by videoconferencing has the potential to reduce barriers to treatment delivery and access including overcoming cost and motivational barriers when patients must travel great distances to seek treatment. This may be an especially important issue in delivering high quality, empirically-validated treatments to low SES populations. Videoconferencing delivery of psychotherapies may also provide greater opportunity for low-income populations to access providers who are trained in empirically-validated therapies and it may allow for more cost-effective delivery of extended treatments which, as noted above, have been found to be more efficacious in the treatment of smoking than standard courses of treatment.

Gaps in Scientific Knowledge and Technical Capacity That Will Be Addressed

As noted above, in-home videoconferencing delivery of evidence-based psychotherapies has been found to be feasible and acceptable when delivered on desktop, laptops and tablets. However, to date there has been less focus on testing video-based psychotherapeutic interventions via smaller screen, portable devices such as smartphones. In

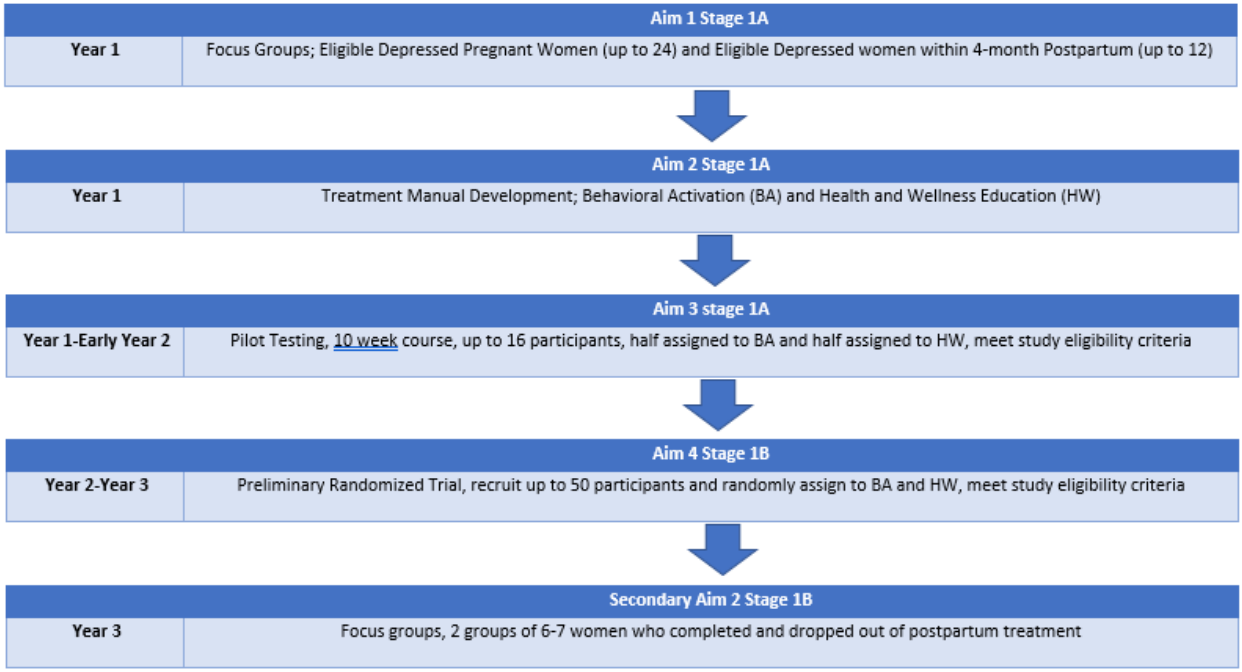
low-income populations, smartphones may serve as the only or primary access that individuals have to access the internet. Given the importance of the therapeutic alliance in predicting symptom reduction in depression treatments,[67] it is especially important to evaluate the quality of the alliance that can be established when BA is delivered by smartphone. In addition, it is not known whether smartphone video and audio quality are adequate for delivery of psychotherapy. Within a research context, it is desirable to conduct screening and study assessments remotely by telephone and smartphone to reduce the need for participants to travel to the research location. This would allow for increased ability to recruit and retain participants and opportunity to evaluate a completely remote delivery of the intervention. However, remote assessment introduces questions concerning measurement integrity and ability to adequately manage psychiatric emergencies. Specific to the targeted population, there are no studies demonstrating the acceptability and feasibility of extending behavioral treatments from the prenatal to postpartum period in low-income pregnant smokers with high levels of depressive symptoms. Women who continue to smoke during pregnancy experience more psychological problems, less paternal social support and more stress associated with family problems, finances, job strain, and unemployment.[19, 68–71] These factors could pose barriers to engaging in treatment over long periods of time, especially when treatment is delivered remotely.

The proposed study will utilize Stage I of the Stage Model of Behavioral Therapies Research to address these research gaps. The Stage Model of Behavioral Therapies, which is supported by National Institute on Drug Abuse, articulates progressive stages of development and evaluation of behavioral interventions. Stage IA is focused on therapy development and manual writing. Stage IB is focused on pilot testing of a final version of the therapy.[72] The figure below depicts the stages of the proposed study by the Stage Model. To increase the generalizability of study findings to the population in which smoking rates are highest during pregnancy and a population that might be actively screened and referred for treatment in the future should the intervention be found to be efficacious, we will recruit participants from antenatal clinics that serve predominantly low income pregnant women, and also recruit from the community, potentially across Texas, using advertising that may include social media, ads, print, or flyers. We will use master level counselor*s* to deliver the interventions and utilize self-report questionnaires to assess important variables which could more easily translate to use in tobacco treatment services. Completion of this study will allow for the evaluation of a number of aspects of feasibility and acceptability of smartphone real-time video delivery of an evidence-based behavioral therapy in a population that previously has been recalcitrant to treatment. Findings will contribute to overall knowledge of the feasibility of delivering intensive behavioral interventions via newly developed technologies and information on BA's effect size for planning of future trials. If BA is found to be efficacious in depressed pregnant smokers in future trials, it could be more broadly disseminated through quit lines and other remotely delivered smoking cessation specialist services.

Investigative Team

The PI, Dr. Janice Blalock, has extensive experience conducting studies evaluating cognitive behavioral interventions for the treatment of depressive and anxiety disorders and comorbid depression and smoking. During her tenure as a clinical assistant professor at University of Texas Medical Branch, she served as a co-investigator and site psychotherapy supervisor on a multi-site study evaluating a combined CBASP and antidepressant medication intervention versus medication and CBASP alone, in the treatment of chronic major depression.[73–82] She was co-principal investigator on our previous clinical trial evaluating CBASP as a smoking cessation intervention for pregnant smokers during the prenatal period (R01 DA14301). She has published and co-authored numerous articles examining treatment of smoking in pregnant women and the impact of depression and other psychological variables on smoking-related outcomes in pregnant smokers.[83–87, 51, 88, 89] Dr. Blalock was also the PI on a

NIMH-funded study (R01 MH076776) and subcontract (1R01MH087692) investigating CBASP as a smoking cessation intervention for chronically depressed smokers.



RESEARCH DESIGN AND METHODS

Aims 1-3 Approach 1 (Stage IA)

Design The overall objective of Aims 1, 2 and 3 is to adapt an existing BA treatment protocol[90] that has been tailored for depressed pregnant women[56] for delivery via real-time videoconferencing on smartphones during the prenatal and postpartum periods. As part of Aim 2, we will adapt these existing BA treatment protocols to create a manual for treatment of depression in the prenatal and postpartum period. We have existing smoking cessation counseling manuals for treatment of pregnant smokers in the prenatal period from a previous trial,[51] which we will extend to the postpartum period. The focus of BA during the postpartum period will be similar to that of the prenatal period—"increasing engagement in rewarding and adaptive activities, decreasing engagement in activities that maintain or increase aversive control (including avoidance) and solving problems that limit access to reward or maintain or increase aversive control."[60] However, there is a need to further develop the smoking cessation counseling treatment for the postpartum period which we will accomplish in this phase of the study.

There is a need to evaluate the feasibility of delivering such therapies by smartphone videoconferencing given the potential for lack of treatment engagement over a smaller screen, use of data plan minutes for extra-treatment activities that deplete minutes available for pending treatment sessions and loss of cell phones. Other areas in need of evaluation include technical issues associated with equipment, need for technical support and remote management of

adverse reactions and psychiatric emergencies. Among pregnant and postpartum women, there may be barriers that impact their ability to participate in numerous therapy sessions over an extended period of time, such as lack of child care and unwillingness/inability to be located in a private area when treatment sessions are scheduled. During stage IA of the project, we will continuously evaluate the data collected, and if we feel that the data collected has provided the information to optimize the treatments and study procedures for AIM 4 (Stage IB), we may begin AIM 4 before we finish AIM 3. .

Aim 1 (Stage IA) and Secondary Aim 2; Research Design

Participants In year 1, we will recruit a) depressed pregnant smokers and; b) depressed women within 4 months postpartum who smoke to participate in individual interviews or in focus groups of up to 12 participants each. Approximately two thirds of the sample (up to 24 participants) will be gestational age up to 36 weeks, and approximately one third (up to 12 participants) will be within 4 months postpartum. Women will be required to meet Stage IA trial eligibility criteria and will be recruited in the same manner as women who will participate in the Stage IB trial (See Section Eligibility criteria and Recruitment sites). Participants will be provided with a smartphone preloaded with an institutionally approved videoconferencing application to reduce barriers to participating in the focus group. They will be able to keep the smartphone following the completion of the focus group (See **Provision of Smartphones and Data Plans)**.

In the case that Covid-19 prevents us from conducting focus groups, we will conduct one-on-one interviews with women who meet the eligibility criteria.

Participant Compensation Participants will be compensated by way of a reloadable gift card; $25 for the completion of the baseline visit and $50 for the completion of the one-time focus group, for a total of $75.

Eligibility Criteria: AIM 1

Inclusion criteria for Aim 1

1) Pregnant (or within 4 months post-partum for aim 1 only)
2) Meets criteria for current Major Depressive Disorder (MDD) as assessed by the Mini International Neuropsychiatric Interview (MINI) 7.0.2 OR PHQ score of 10 or greater.
3) ≥ 18 years of age
4) Have a telephone
5) Self report smoking, even a puff, cigarettes, little cigars and/or cigarillos in the past 30 days.
6) Approximately two thirds of the sample will be gestational age up to 36 weeks, and approximately one third will be within 4 months postpartum

7) Able to speak and read English

8) Subjects must report a current residence in the State of Texas

Exclusion criteria for Aims 1

1) Rated on the Columbia-Suicide Severity Rating Scale[113] at screening as in the past month having had active suicidal ideation with some intent to act or active suicidal ideation with specific plan and intent (indicated by answering "YES" on both Q3 and Q4, and/or 5) and/or endorsing "YES" to having engaged in preparatory acts towards or attempting suicide in the past 3 months (as indicated by answering "YES" to both parts of Q6)

2) Have a lifetime or current diagnosis of Psychotic Disorder as assessed by specified Mini International Neuropsychiatric Interview (MINI) 7.0.2 modules.

3) Have a past or current diagnosis of Bipolar Disorder I or II or have a past or current diagnosis of Other specified Bipolar and related disorder as assessed by specified MINI 7.0.2 modules.
4) Any otherwise not specified medical or psychiatric condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
5) Participant considered by the investigator as unsuitable candidate for full participation in the study.

Refer to sections Participant Recruitment (Aim 1, 3, 4), Pre-Screening Assessment (AIM 1, 3, 4), Informed Consent Process (AIM 1, 3, 4), Baseline Screening Phone Visit (AIM 1, 3, 4) for detailed information of the enrollment process.

Focus Group Procedures and Data Analysis Objectives of Aim 1 are to collect qualitative data on a) barriers and supports to completing treatment sessions and study assessments; b) suggestions for decreasing barriers to treatment engagement and increasing treatment acceptability; and c) usefulness of BA, HW and smoking cessation counseling treatment materials that will include pregnancy specific materials that focus on the prenatal and postpartum period (*Forever Free…For Baby and Me*),[91] and; d) usefulness and acceptability of the BA app, supportive HW app messages and supportive smoking cessation messages. Examples of smoking cessation counseling material specific to the postpartum period include: ways that smoking abstinence improves the health of the newborn and risks of second and third hand smoke to infants and children, management of stress and negative moods related to birth and new motherhood, use of alcohol as a risk-factor in the postpartum period, hormonal changes after birth, effect of smoking on breastfeeding and benefits of breastfeeding, lifestyle balance as a protection against relapse, and coping with weight gain using non-smoking strategies. Individual interview or focus group participants will also view a sample list of Health and Wellness topics and a video sample of BA techniques (refer to study document 'Ppt HW Manual Contents')

Given that our focus is on low-income women, we will include specific questions on variables frequently noted in low-income women who smoke that may present barriers to successful cessation and treatment engagement (refer to study document 'Focus Group Questionnaire'). Women who continue to smoke during pregnancy are more impoverished, more nicotine dependent, have more smokers in their social network, are more likely to consume alcohol during pregnancy, to be single and to have an unintended pregnancy than those who quit.[92, 68, 93, 71, 94] They experience more psychological problems, less paternal social support, lower self-efficacy for coping with daily stressors, and more stress associated with family problems, finances, job strain, unemployment, and physical and sexual violence.[19, 68–71] Similar smoking and demographic factors are associated with postpartum relapse or smoking.[95–101] We will use findings from these questions to inform the development of the prenatal and postpartum smoking cessation materials and the BA treatment protocol.

Focus groups or individual interviews will be conducted by experienced staff who are part of the Assessment, Intervention and Measurement (AIM) Shared Resource at MD Anderson Cancer Center, via institutionally approved videoconferencing software. This shared resource provides specialized research support, including collection and analysis of data from focus groups. Dr. Yolanda Villarreal will provide expertise on focus group implementation and qualitative data analyses. For the proposed study, AIM staff and Dr. Blalock will consult with Dr. Villarreal in developing focus group semi-structured interview protocols. AIM personnel, which

may include both a facilitator and note-taker, will conduct these focus groups, composed by criterion-based network sampling.[102]

Focus Group/Individual interview Data Analysis Focus groups or individual interviews will be recorded with a digital audio recorder and professionally transcribed. Recordings and transcripts will be stored in REDCap and will be destroyed within 1 year of the end of the study. Each transcript will be validated by the staff person who conducted the interview to assure accurate and complete transcription. With Dr. Blalock as cross-reader, Dr. Villarreal will work with readers (i.e., AIM staff) to code transcripts for overarching themes, supported by ATLAS.ti qualitative data analysis software, using conventional grounded theory methodology (identifying categories that capture the basic aspects of the group's experience).[103] Specifically, data analysis will focus on the intervention adaptation content and considerations identified by focus group and individual interview participants. Data analysis will consist of the 3 phases of "constant comparison".[104,105, 106] In their coding, the readers will consider five established criteria recommended by Krueger:[107] frequency, specificity of responses, emotions, extensiveness, and big picture. The focus group or individual interview transcript will be read and discussed by the team of readers to identify initial ideas for treatment modifications and improvements. The transcript will then be coded using the domains identified by the team but also using open coding to identify additional details for intervention improvements. Readers will discuss their coding to consensus and present results to the PI and co-Investigators. Dr. Villarreal will organize identified concepts that emerged from coding into themes with a particular focus on improvements for the intervention. A summary of the focus group and individual interviews results and a revised manual will be sent to the external auditor, Dr. Angela Stotts, an expert in the field of smoking cessation interventions for women in the prenatal and postpartum periods. The role of the external auditor is to provide an expert point of view from a professional not involved in the study's data collection or analysis, in a qualitative form of testing reliability and convergent validity.[108] Dr. Stotts will comment briefly, in writing or audio recording, on the consistency of each theme with her knowledge of the area; her comments will be incorporated into Dr. Villarreal's full report on the results which will be used to develop the adapted treatment materials.

Given Drs. Villareal and Stott's role in analyzing the focus group and individual interview data, they may have access to protected health information of focus group participants through listening to audio recorded focus group or individual interview sessions that will include voice prints. This has been noted in the consent document for Aim 1 and Secondary Aim 2.

Aim 2 (Stage IA) Research Design

Treatment Manual Development In year 1, our BA expert consultant Dr. Hubley will draft an initial version of the prenatal and postpartum BA treatment manual (Appendix BA Participant Manual. The BA Counselor Manual (Appendix Counslor BA Manual) is a comprehensive Behavioral Activation treatment guide developed by investigators at the University of Colorado Boulder. The original manual was designed to lead eight (8), 60-minute counseling sessions with the target population. The protocol delivery in AIM 3 is for ten (10), 45-minute counseling sessions. The protocol delivery in AIM 4 is for ten (10) prenatal, four (4) postpartum 45-minute counseling sessions. This treatment manual is organized into meetings designed to coincide with the treatment sessions. The sections were designed for a discussion of the material, not merely didactic instruction. The structure of each meeting is somewhat loose so that the level of emphasis on each component can be tailored to the needs of the individual. Meeting topics can be re-visited in any session as the need arises. Sessions that extend beyond those mentioned in the manual will follow a similar outline and content. Dr. Blalock and the study therapists will modify an existing prepartum version of HW (from a previous study with pregnant smokers[51])

and draft an initial version of a postpartum HW control condition (Appendix . HW Participant Manual). To ensure that the HW condition focuses exclusively on health-related psychoeducation and prohibits discussion of affective-related materials, modifications to the HW manual will include removal of all affective focused materials (e.g., depression, stress) and replacement with health-related materials. Dr. Blalock and the therapists will also modify an existing version of a smoking cessation counseling treatment manual and draft an initial version of the postpartum smoking cessation treatment manual. We will draw from health-related and postpartum smoking cessation material currently under development for a service project that is focused on low-income pregnant smokers in Northeast Texas (CPRIT PP180077, PI: Blalock). We will utilize feedback from the focus group/individual interview data analysis to further modify treatment materials to increase acceptability and applicability of the BA and HW treatments. Dr. Hubley will adapt the existing Quality of Behavioral Activation Scale, the BA fidelity tool developed at the University of Colorado for use in clinical trials. This may be used in the certification of the therapists in AIM 2 (Stage IA). Dr. Hubley will adapt the Review of Alma Mentoring for Peers (RAMP) form, the BA fidelity tool developed at the University of Colorado for use in clinical trials to be used in AIMs 3 and 4. Dr. Blalock and the study therapists will modify existing HW and smoking cessation scales used in our previous study with pregnant smokers, to reflect changes in treatment protocols. These scales will be used to monitor therapist adherence and competence during the preliminary pilot AIM 3 (Stage IA) work and the AIM 4 (Stage IB) trial. Dr. Hubley will train Dr. Blalock in the use of the BA fidelity rating forms.

Aim 3 (Stage IA) Research Design

Participants In years 1 and 2, we will recruit up to 16 participants (half assigned to BA and half assigned to HW who meet the study eligibility criteria (see section Eligibility Criteria), with the exception that we will attempt to recruit women who are between 12 to 34 weeks in gestational age.. This will allow us to pilot test a 10-week course of treatment for BA and HW that may extend into the postpartum period for some women depending on their gestational age at the time of study entry. The participants will be seen during years 1 and 2. Women who participated in focus groups or individual interviews who meet the gestational age eligibility criterion will be offered the opportunity to participate. To encourage completion of screening and treatment sessions, which will allow for more complete collection of pilot data from this limited number of participants, we will compensate women for completing all required questionnaires and applicable samples at each visit. Compensation is as follows: $25 for screening visit, $30 for Visit 1, and $20 for V2-V10, for a possible total of $235.

Therapist Training In an effort to ensure cultural competence of therapists, study therapists will be required to take a cultural competence course as part of their training. During year 1, Dr. Blalock and the therapists will complete a virtual in-person training conducted by Dr. Hubley. This training will include didactic sessions, readings, familiarization with treatment and fidelity rating forms and role playing of BA skills. The therapists will be master level counselors. Dr. Hubley will work with Dr. Blalock to develop an ongoing training and supervision plan. Using this plan and under the guidance of Dr. Hubley, Drs. Blalock and Hubley or Dr. Blalock will meet with the study therapists on a regular basis for supervision, during Aim 3 treatment delivery and Aim 4 randomized trial treatment delivery. A licensed psychologist or a PI designee will oversee training in HW. Following the BA virtual in-person training and initial pre-certification, and HW training, Dr. Blalock will deliver the abbreviated 10-session BA protocol to one Stage IA pilot participant. The therapists will deliver both BA and HW 10-session protocols to Stage IA pilot participants. Each session will be videotaped. Dr. Hubley will provide fidelity ratings on Dr. Blalock's case and will also provide ratings and feedback on the therapist cases. Dr. Blalock

and Dr. Hubley will complete ratings of BA fidelity, and Dr. Hubley will provide further guidance to Dr. Blalock on these ratings. A licensed psychologist or a PI designee will complete ratings of Smoking Cessation behavioral counseling and HW treatment and adherence. Regular supervisory feedback to the study therapists will be based on Drs. Hubley and the PI designees viewing of taped sessions and their ratings on the fidelity scales. Supervisory feedback during the Stage IB trial will be based on ratings of videotaped sessions in both conditions. Dr. Hubley will continue to provide guidance to Dr. Blalock and study therapists throughout the Stage IB trial.

Therapist Certification The modified BA, HW and smoking cessation prenatal/ postpartum treatment rating scales will be utilized to certify Dr. Blalock's and therapists' adherence and competence following delivery of treatment during mock sessions in AIM 2 (Stage IA) and to monitor therapist adherence and competence during the Stage IA preliminary pilot and Stage IB trial. The exact rating form to be used will be determined by the rater and the PI. Additional minor changes may be made to the form in the future based on ongoing discussions between the PI and the raters. If substantive changes are made, the updated form will be re-submitted for IRB review (See Appendix. BA Rating Form for a sample rating form). Fidelity to the BA intervention will be assessed based on Dr. Hubley's ratings of 2 randomly selected sessions of AIM 2, Stage IA cases to certify therapists who meet standards in the delivery of BA (operationalized as a mean score of 3 on the rating scale). Similarly, for the HW intervention, a PI designee will rate 2 sessions of the AIM 2 (Stage IA) mock cases to certify therapists' who meet standards in the delivery of HW (operationalized as a mean score of 3 on the HW rating scale).

Preliminary Pilot Testing Procedures The objectives of Aim 3 are to pilot test delivery, via smartphone videoconferencing, of a 10-week treatment course of smartphone delivery of BA and HW and to conduct process evaluation of technical issues in use of smartphones, barriers to participation and retention; assessment burden, and adequacy of procedures for addressing psychiatric emergencies. To provide preliminary assessment of smartphone and data plans in these participants, we will include assessment of these variables during this phase of the study.

Participants may be provided with headphones, if they want them, to ensure privacy of therapy session discussions with the therapist. Women will be allowed to keep the headphones. During years 1-2, up to 16 participants (half each assigned to BA and HW) will be screened and enrolled in the study, according to procedures listed in the Eligibility Criteria We will abbreviate therapist manuals and treatment materials to a 10-session protocol that may span both prenatal and postpartum periods, depending on the participant's gestational age at the time of study entry. This will allow us to conduct preliminary testing of treatment delivery within the time constraints of a 3-year study. The BA and HW treatments will be delivered by Dr. Blalock and the study therapist*s*. During years1-2, the investigative team (Drs. Blalock, Hubley, and Villarreal) will meet regularly with the study therapist*s* to discuss results of process measures from the participants and overall impressions of needed changes in study treatment and procedures. Prior to running the randomized trial, we will modify these changes in addition to any technical and study procedures, study materials and biochemical verification strategies.

Given Dr. Hubley's and other PI designees role in training and supervising the study therapists through viewing of videotaped counseling sessions, as external collaborators they will have access to participants' protected health information. This has been noted in the consent document for this aim.

Visit Windows We will aim to schedule Visit 1 randomization approximately 1 week following baselines, but may be delayed due to various reasons including but not limited to the following: a) medical findings that may be significant but not exclusionary, b) participant-related events (e.g., travel, work schedules), or c) study related factors (e.g., full clinic schedule).

In these cases where a visit is delayed past 30 days, a re-review of any eligibility criteria will be determined on a case by case basis. If there are no significant changes, participants will be allowed to continue to randomization as described above. If there are significant changes, the baseline and psychiatric screening process will be conducted again as deemed appropriate by PI.

Starting at V2 through V10, there will be a +5 calendar days window. Given that women coming in at later gestational ages will give birth during their time in treatment, flexibility in scheduling will be allowed without having to log deviations. If the woman gives birth during the treatment visits, we will allow their next visit window to be extended an additional 5 calendar days in order to reschedule the visit, for a total of + 10 calendar days.

Eligibility Criteria: AIM 3

Inclusion criteria for Aims 3

1) Meets criteria for current Major Depressive Disorder (MDD) as assessed by the Mini International Neuropsychiatric Interview (MINI) 7.0.2 OR PHQ score of 10 or greater.
2) ≥ 18 years of age
3) Have an address and telephone number where they may be reached
4) Self report smoking, even a puff, cigarettes, little cigars and/or cigarillos in the past 30 days.
5) Gestational age between 12 to 34 weeks

6) Able to speak and follow verbal and written instructions in English
7) Subjects must report a current residence in the State of Texas and must not have plans to move out of the state in the next 2.5 months

8) Subjects referred directly from UT Health providers, the provider or designee will confirm pregnancy status through their electronic health record prior to the referral. Subjects referred by any other means will confirm positive pregnancy status through an at-home test.

9) Willing to refrain from the use of other nicotine/tobacco products for the duration of the study

10) Agree to be treated via telehealth (live audio-video conference and phone) and to be contacted via text and/or email
11) Provide informed consent and agree to all assessments and study procedures

Exclusion criteria for Aim 3

1) Currently participating in individual psychotherapy
2) Currently participating in other smoking cessation treatments and refuses to refrain from use for the duration of the study
3) Rated on the Columbia-Suicide Severity Rating Scale[113] at screening as in the past month having had active suicidal ideation with some intent to act or active suicidal ideation with specific plan and intent (indicated by answering “YES” on both Q3 and Q4, and/or 5) and/or endorsing “YES” to having engaged in preparatory acts towards or attempting suicide in the past 3 months (as indicated by answering “YES” to both parts of Q6)

4) Have a lifetime or current diagnosis of Psychotic Disorder as assessed by specified Mini International Neuropsychiatric Interview (MINI) 7.0.2 modules.
5) Have a past or current diagnosis of Bipolar Disorder I or II or have a past or current diagnosis of Other specified Bipolar and related disorder as assessed by specified MINI 7.0.2 modules.
6)Any otherwise not specified medical or psychiatric condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
7) Participant considered by the investigator as unsuitable candidate for full participation in the study.

Refer to Table 1 & Table 2 (Prenatal & Postpartum) for the full schedule of assessments, and more details in section AIM 3 and AIM 4 Assessments.

Refer to sections Participant Recruitment (Aim 1, 3, 4), Pre-Screening Assessment (AIM 1, 3, 4), Informed Consent Process (AIM 1, 3, 4), Baseline Screening Phone Visit (AIM 1, 3, 4) for detailed information of the enrollment process.

Aim 4 Approach (Stage IB)

Design The objective of Aim 4 is to conduct a preliminary randomized trial to evaluate the effect of BA on abstinence and depression at 4 ½ months postpartum; to demonstrate the feasibility of the smartphone-delivered BA intervention for depressed pregnant smokers during prenatal and through 2 ½ months postpartum, and feasibility of study procedures. We will recruit pregnant smokers in the same manner as AIM 3 (Stage IA). We will employ a randomized, controlled between groups design in which depressed pregnant smokers will be randomly assigned, using a form of adaptive randomization called minimization,[112] to either BA or HW. We will stratify treatment assignment by baseline depression, smoking rate and gestational age. The data that are collected will be used to support feasibility of delivering a prenatal and postpartum intervention to depressed pregnant smokers via smartphone and to provide estimates of effect size for planning future fully-powered trials.
Participants We will recruit up to 50 depressed pregnant smokers who are between 18 to 32 weeks gestational age in their pregnancies.

Compensation AIM 4

We will pay women in the Stage IB randomized trial up to $25 for completion of the baseline screening visit, $65 for completion of the end of prenatal treatment assessment, end of postpartum treatment assessment (2 ½ months) If the participant is lost to follow-up in either the prenatal or postpartum period or did not complete all visits during those timeframes, they will be compensated for the final visit that was completed. Given the variability in timing for each individual participant, if this scenario occurs payment may be delayed until the final visit is verified)) and the 4 ½ months postpartum assessment, with the possibility of $220 in total compensation.

Feasibility of Recruitment As indicated in Dr. Refuerzo''s letter of support, the UT OB/GYN faculty provide clinical care at multiple clinics that will serve as recruitment sites for this study. A total of approximately 4,574 births per year to predominantly low-income women are under UT faculty care. Based on a study that was recently conducted in a UT clinic that is similar to clinics from which we will be recruiting, 14% of women identified as smokers.[89] A

study using a nationally representative survey found that among women who smoked cigarettes during pregnancy, 12.4% met criteria for a mood disorder and 37.3% of women with nicotine dependence had a mood disorder. Using the estimate of 14% smoking from the UT clinic study and national findings on percent of women with depressive disorders, we conservatively estimate that 25% of the 640 women who smoke will meet our depression criteria of scoring ≥ 10 on the Patient History Questionnaire 9 (PHQ-9) each year. Using these percentages, we estimate that 160 women would meet our criteria per year and that 50% would meet all eligibility criteria and consent to participate, providing around 80 women per year who would be eligible. Thus, we feel confident that we will be able to recruit up to 21 women who meet our eligibility criteria for Stage IA focus groups during year 1; up to 16 women for Stage IA pilot work during year 1 and early year 2, and; up to -50 women for Stage IB work during year 3.

Eligibility Criteria: AIM 4

Inclusion criteria for AIM 4

1) Meets criteria for current Major Depressive Disorder (MDD) as assessed by the Mini International Neuropsychiatric Interview (MINI) 7.0.2 OR PHQ score of 10 or greater.
2) ≥ 18 years of age
3) Have an address and telephone number where they may be reached
4) Self report smoking, even a puff, cigarettes, little cigars and/or cigarillos in the past 30 days.
5) Gestational age between 18to 32 weeks
6) Able to speak and follow verbal and written instructions in English
7) Subjects must report a current residence in the State of Texas and must not have plans to move out of the state in the next 7-8 months
8) Subjects will confirm positive pregnancy status through study provided pregnancy test or provide paperwork verifying pregnancy status if the pregnancy test is inconclusive
9) Willing to refrain from the use of other nicotine/tobacco products for the duration of the study
10) Agree to be treated via telehealth (live audio-video conference and phone) and to be contacted via text and/or email
11) Provide informed consent and agree to all assessments and study procedures
12) Interested in treatment that might change smoking behavior or help them quit smoking
13) Be the only participant in their household currently receiving treatment on this protocol

Exclusion criteria for Aim 4

1) Currently participating in individual psychotherapy
2) Currently participating in other smoking cessation treatments and refuses to refrain from use for the duration of the study
3) Rated on the Columbia-Suicide Severity Rating Scale[113] at screening as in the past month having had active suicidal ideation with some intent to act or active suicidal ideation with specific plan and intent (indicated by answering “YES” on both Q3 and Q4, and/or 5) and/or endorsing “YES” to having engaged in preparatory acts towards or attempting suicide in the past 3 months (as indicated by answering “YES” to both parts of Q6)
4) Have a lifetime or current diagnosis of Psychotic Disorder as assessed by specified Mini International Neuropsychiatric Interview (MINI) 7.0.2 modules.

5) Have a past or current diagnosis of Bipolar Disorder I or II or have a past or current diagnosis of Other specified Bipolar and related disorder as assessed by specified MINI 7.0.2 modules.
6) Any otherwise not specified medical or psychiatric condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
7) Participant considered by the investigator as unsuitable candidate for full participation in the study.

Inclusion criterion for Secondary Aim 2, Stage IB
Women enrolled in the study who dropped out of the study during the first month of the postpartum treatment phase or women who completed at least 3 of the 4 postpartum treatment sessions

Because study therapists will be asked to complete the WAI and acceptability of treatment ratings as part of Aim 4 work, they will be considered study participants and will provide verbal consent to complete these measures.

Inclusion criterion for Study Therapists

1. Masters degree in psychology, social work, or other counseling degree
2. Training in the delivery of psychotherapy and counseling interventions

Participant Recruitment (Aim 1, 3, 4)
We have established a subcontract with The University of Texas Health Science Center at Houston (UTHSC) to assist us with recruitment. The PI, Dr. Jerrie Refuerzo, is an Associate Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences, McGovern Medical School—UT Health (see Letter of Support).

Designated staff will conduct a pre-screen of women who may be identified as potentially eligible. This pool of candidates are women being seen in multiple large clinics staffed by UT OB/GYN faculty for depression and smoking eligibility(see Feasibility of Recruitment and Pre-Screen Assessment Script), and also self-referrals from community advertising, which may include but not limited to social media, radio, digital and print ads. We may also utilize mailing lists that target our audience to send IRB approved post-cards.

Study participants will be individuals residing in the State of Texas. Recruitment efforts may include direct mail from registries, mailing flyers, public service announcements, media interviews, and advertisements on online social media, radio, television, digital media and recruitment companies, and newspaper outlets. Institutional channels may be used to aid study recruitment, including, but not limited to, patient database data mining (e.g., EPIC, TRTP database) for potentially eligible patients and other internal recruitment methods (e.g., MyChart to send messages, newsletters, inside MD Anderson television channels). The Tobacco Research and Treatment Program's web screener database for tobacco users, outlined in IRB-approved PA18-0423, also may be used as a recruitment source for this study. This database houses data collected from an internet-based screening questionnaire to recruit tobacco users from the Houston area, as well as across Texas more broadly, who may be interested in participating in tobacco use and cessation studies at MD Anderson Cancer Center. PA18-0423 allows the sharing of data with IRB-approved MD Anderson protocols. We will rotate through various venues throughout the recruitment period. We have many years of experience using these venues for quitting and nonquitting tobacco clinical trials recruitment. The MD Anderson Marketing and Communications departments may also assist in arranging interviews, public service announcements, and social media communications to assist in study recruitment.

Additionally, we may engage the services of external clinical trials recruitment services to obtain contact information of prospective study participants.

Pre-Screening Assessment (AIM 1, 3, 4) All participants across Aims 1,3 and 4 will be prescreened by telephone or in person for basic eligibility requirements (refer to study document Appendix Pre-Screen Assessment). The pre-screening assessment will be performed by a delegated and trained collaborator from The University of Texas Health Science Center or a staff member from MD Anderson. This may be done over the phone or in-person. An initial description of the study design will be provided, and demographic data will be collected, as well as concomitant medications, current smoking and other nicotine/tobacco use, current/recent treatments for tobacco use, pregnancy status, and current psychotherapy involvement. Data collected will be in a shared database between UT Health and MD Anderson. Responses to the phone screen questions will be used to determine initial eligibility.

All participants who remain eligible after pre-screening will then be scheduled to meet with a clinician for their Baseline screening telephone visit where the study requirements will be explained in more detail and the Informed Consent Document reviewed and signed (see Informed Consent Process for details). A set of questionnaires will be sent to the participant approximately 5 days prior to the scheduled visit and they will be asked to complete the assessments prior to the telephone baseline screening visit. Since the questionnaires contain information required to determine eligibility, staff may send extra prompts via text, email or phone call to the participant to complete the assessments prior to the visit. As a last resort, participants will be informed that this screening visit may be rescheduled if they are unable to complete the assessments prior to the visit.

Informed Consent Process (AIM 1, 3, 4) Separate consent documents have been developed for Aims 1, 3 and 4. Participants may receive a copy of the Informed Consent Document electronically prior to their baseline screening phone visit which they may review prior to their scheduled visit and prepare questions. If the participant does not have a valid email address, we will not send the consent document. At the baseline screening phone visit a trained staff member will verbally review the consent document with the participant. Participants will have the opportunity to ask questions about the consent document or other study-related assessments and procedures prior to consenting to continue screening. If the participant agrees to participate in the screening process and the study:

Aim 1: the participant will give their verbal agreement to proceed. The study staff will then sign the verbal consent document and document the consenting process in RedCap. A verbal consent is used in this aim because it may not be practical (feasible) to obtain signed authorization from these participants as our interactions with them are restricted to video conferenced focus groups and requiring a process to obtain a signature would create a barrier to recruitment; it may bias the sample that is recruited for the study if a signature is required, given that this may include a low income population that is likely to be burdened by child care needs, financial stressors, etc. A written consent may lead to women who are not experiencing these burdens to volunteer. Participants will be registered in the institutional database (CORe) within two business days of providing verbal consent to engage in Baseline Screening procedures.

Aim 3: The consent process will be a two-stage consent process. The participant will give their verbal agreement to proceed. The study staff will then sign the verbal consent document and document the consenting process in the study database. A verbal screening

consent is used because it may not be practical (feasible) to obtain signed authorization from these participants as our interactions with them at the screening visit are restricted to telephone. Requiring a process to obtain a signature would create a barrier to recruitment; it may bias the sample that is recruited for the study if a signature is required, given that this may include a low income population that is likely to be burdened by child care needs, financial stressors, etc. Participants will be registered in the institutional database (OnCORE) within two business days of providing verbal consent to engage in Baseline Screening procedures.

At V1, the main treatment informed consent document will be sent to the participant via a link, which will be pushed through DocuSign, via text and/or email. They will be asked to electronically sign the document before proceeding. Following the participant signature, study staff will then sign the consenting document and document the consenting process in the study database. Participants will be registered and assigned to treatment in the institutional database (OnCORE) within two business days of signing consent.

The verbal consents for all Aims will cover the eligibility screening assessments, including the review of the pre-screening assessment and information provided in the questionnaires, and will make clear that by consenting to proceed does not mean they are eligible to participate in the study. The Consent documents will also cover the details of study participation specific to each Aim.

Aim 4: At the baseline screening visit, the informed consent document will be sent to the participant via a link, which will be pushed through DocuSign, via text and/or email. They will be asked to electronically sign the document before proceeding. Following the participant signature, study staff will then sign the consenting document and document the consenting process in the study database. Participants will be registered in the institutional database (OnCORE) within two business days of signing consent.

The consent for Aim 4 will cover the eligibility screening assessments, including the review of the pre-screening assessment and information provided in the questionnaires, and will make clear that by consenting to proceed does not mean they are eligible to participate in the study. The Consent documents will also cover the details of study participation specific to each Aim.

Baseline Screening Phone Visit (AIM 1, 3, 4) At the baseline screening phone visit (V0), which will ideally occur within 30 days of the pre-screen visit, study participants may be asked to verify information provided at the pre-screening assessment to verify that there have not been any changes since completion. A trained staff member will then complete the consenting process (described above). Once the participant has provided their consent, a Master's level counselor will then administer the remaining screening psychiatric assessments, the Mini International Neuropsychiatric Interview (MINI) 7.0.2, the Columbia-Suicide Severity Rating Scale (C-SSRS)[113] and the Patient Health Questionnaire (PHQ-9). In AIM 4, the PHQ will be administered through Qualtrics, except for Question 9 pertaining to suicidal ideation, which will be asked by the clinician during the visit. Aims 3 and 4 will have additional screening measures, including but not limited to a brief relevant medical history (Appendix Medical History), medication use (Appendix. CCMs & Other Smoking Cessation Medications_Treatments & Other Psychotherapy Form) , smoking history (Appendix. Baseline Demographic & Smoking History), current nicotine/tobacco use (Appendix. TFBI), measure to assess anxiety (Appendix. GAD-7), childhood trauma (Appendix. Childhood Trauma Questionnaire), dependence on tobacco

(Appendix. FTND), positive and negative affect (Appendix. PANAS), and cognitive function (Appendix. PROMIS) (See **Table 1 & Table 2 (Prenatal & Postpartum)**. Screening Assessment Schedule). If a participant reports severe depressive and/or anxiety symptoms or suicidal ideation on the PHQ-9 and/or C-SSRS, a designated senior clinician, clinical psychologist, and/or the study physician/medical team will be consulted for further assessment, evaluation, intervention, or referral to treatment as clinically appropriate per standard of care. Additionally, participants whose depressive disorders or other psychiatric symptoms/disorders place them at high risk for self-harm will be excluded from the study. The PI or her designee may review these symptoms with the participant to determine the need for outside community referral and/or a referral back to Dr. Refuerzo and team if they were the referring provider, who will handle any moderate to severe psychological and/or pregnancy symptoms of concern, as deemed necessary by the delegated mental health practitioners (MHPs).

Participants who remain eligible following the completion of the baseline screening assessments will be:

AIM 1: enrolled or randomized into the study and mailed a smartphone, headphone set, and reloadable gift card. The participant will be scheduled for an equipment check call (to test their study phone and the videoconferencing platform to work out any technical issues) prior to the individual interview or focus group session (Aim 1).

AIMs 3: mailed a welcome study kit including a smartphone, headphone set if the ppt wishes to have them, a reloadable gift card, welcome letter, compensation scheme, staff contacts list, zoom instructions, and if applicable, a pregnancy collection kit. The participant will be scheduled for an equipment check call to test their study phone and the videoconferencing platform to work out any technical issues prior to their first treatment visit. After signing the main treatment consent at visit 1, the participant will be enrolled into the study. The participant will be mailed a second kit containing urine cotinine collection kits and instructions, a smoking cessation participant manual, and their assigned participant treatment manual and additional resources.

The study-specific supplies will be shipped to eligible participants and tracked through eShipGlobal or a comparable system within two business days of completion of the Baseline Screening visit.

If a person is deemed ineligible, she will be notified and may be referred to her physician for local medical/psychiatric care for follow-up, if applicable. Resource information may be provided to a participant if deemed appropriate (Appendices: Texas FQHC list, Texas Mental Health Resources, Texas Sheriff's Departments, Texas Domestic Violence Resources, Smoking Cessation Resources). These resources are intended to be living documents and may be updated in real time if we learn that some of the resources are outdated, or new resources are identified, etc.

AIM 4: mailed a welcome study kit including a smartphone, headphones if the ppt requests them, a reloadable gift card, welcome letter, compensation scheme, staff contacts list, zoom instructions, and a pregnancy collection kit. The participant will be scheduled for an equipment check call to test their study phone and the videoconferencing platform to work out any technical issues prior to their first treatment visit. At Visit 1, after a review of information for final eligibility, if participant remains eligible, she will be randomized into the study. The participant

will be mailed a second kit containing urine collection kits and instructions, a smoking cessation participant manual, their assigned participant treatment materials and additional resources.

The study-specific supplies will be shipped to eligible participants and tracked through eShipGlobal or a comparable system within two business days of completion of the Baseline Screening visit and Visit 1.

If a person is deemed ineligible, she will be notified and may be referred to her physician for local medical/psychiatric care for follow-up, if applicable. Resource information may be provided to a participant if deemed appropriate (Appendices: Texas FQHC list, Texas Mental Health Resources, Texas Sheriff's Departments, Texas Domestic Violence Resources, Smoking Cessation Resources). These resources are intended to be living documents and may be updated in real time if we learn that some of the resources are outdated, or new resources are identified, etc.

AIM 1 & 3: Table 1

	Pre-Screening Assesment		Baseline Screening Phone Visit (V0)		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 EOT
Timeline					day 1 of treatment	Weekly Treatment Visits								
Beginnin of Treatment Week					1	2	3	4	5	6	7	8	9	10
Ideal Days from V1		-14		-7	0	7	14	21	28	35	49	56	63	70
Table 1. Screening Assessment Schedule	AIM 1	AIM 3	AIM 1	AIM 3	AIM 3									
Telephone script & screen (basic eligiblity)	x	x												
Informed Consent verbal/signed			x	x										
MINI*			x	x										
Childhood Trauma Questionnaire				x										
C-SSRS***			x	x										
TLFB				x	x	x	x	x	x	x	x	x	x	x
FTND				x										
Smoking History Form				x										
Medical History				x										
Urine Cotinine Test**						x	x	x	x	x	x	x	x	x
Urine Pregnancy Test				x										
Concomitant Medications (other smoking cessation treatments)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OUTCOME MEASURES														
PHQ-9			x	x	x	x	x	x	x	x	x	x	x	x
GAD-7				x	x	x	x	x	x	x	x	x	x	x
NICOTINE WITHDRAWAL														
WSWS-28					x	x	x	x	x	x	x	x	x	x
MEDIATORS														
PANAS				x	x	x	x	x	x	x	x	x	x	x
PROMIS Cognitive function-abilities				x	x	x	x	x	x	x	x	x	x	x
OTHER														
Counseling					x	x	x	x	x	x	x	x	x	x
Adverse Events					x	x	x	x	x	x	x	x	x	x
WAI-Client Short						x		x		x		x		x
PROCESS EVALUATION														
Technical issues questionnaire					x	x	x	x	x	x	x	x	x	x
Barriers to participation interview														x
Assessment Burden questionnaire							x							x

* MINI Modules: (A, C, D, E, F, G, H, K, N, O)
**Urine cotinine test will be done at visits where the participant is reporting abstinence and meeting the 7 day point prevalence criteria
***C-SSRS may be done at any visits as clinically indicated by the Safety Plan

AIM 4: Table 2. Prenatal:

Timeline			day 1 of treatment	Prenatal visits (PN)									1 month break after birth of baby
Beginning of Treatment Week			Prenatal visits for GA 18-22 weeks = 10 visits over 16 weeks Prenatal visits for GA 23-32 weeks = 10 visits over 12 weeks										
	Pre-Screenign Assessment	Baseline Screening Phone Visit (V0)	PN1	PN2	PN3	PN4	PN5	PN6	PN7	PN8	PN9	PN10	BIRTH
Table 2. Screening Assessment Schedule	AIM 4	AIM 4											
Telephone script & screen (basic eligiblity)	x												
Informed Consent verbal/signed		x											
MINI (a)		x											
Childhood Trauma Questionnaire		x											
C-SSRS (b)		x											
TLFB		x	x	x	x	x	x	x	x	x	x	x	
FTND		x											
Smoking History Form		x											
Medical History		x											
Urine Test (urine cotinine and/or anabasine collection) - (c)				x	x	x	x	x	x	x	x	x	
Urine pregnancy test (d)		x											
Concomitant Medications, Other smoking cessation medications_ treatments & other Psychotherapy	x	x	x	x	x	x	x	x	x	x	x	x	
OUTCOME MEASURES													
PHQ-9		x	x	x	x	x	x	x	x	x	x	x	
GAD-7		x	x	x	x	x	x	x	x	x	x	x	
NICOTINE WITHDRAWAL													
WSWS-28			x	x	x	x	x	x	x	x	x	x	
MEDIATORS													
PANAS		x	x	x	x	x	x	x	x	x	x	x	
PROMIS Cognitive function-abilities		x	x	x	x	x	x	x	x	x	x	x	
OTHER													
Counseling			x	x	x	x	x	x	x	x	x	x	
Adverse Events			x	x	x	x	x	x	x	x	x	x	
Assessment of Changes since last visit			x	x	x	x	x	x	x	x	x	x	
FEASIBILITY MEASURES													
WAI-Client Short				x		x		x		x		x	
WAI - Therapist				x		x		x		x		x	
Technical issues questionnaire			x	x	x	x	x	x	x	x	x	x	
Acceptability of treatment -				x	x	x	x	x	x	x	x	x	
Acceptability of treatment - Clinician													

(a). MINI Modules: (A, C, D, E, F, G, H, K, N, O)
(b). C-SSRS may be done at any visits as clinicially indicated by the Safety Plan
(c). Urine test (cotinine and/or anabasine) will be done at visits where the participant is reporting abstinence and meeting the 7 day point prevalence criteria.
(d). Urine pregnancy test, or if preg test result inconclusive submit paperwork verifying pregnancy
(e). Follow up on any open CCMs/Psychothearpy/Treatments & AEs ONLY
(f). Administer Participant Acceptability of treatment if ppt did not complete at previous timepoints
(g). Clinician Acceptability of treatment may be completed earlier if ppt withdrawals from the study

AIM 4: Table 2. Postpartum

Timeline	1 month break after birth of baby	Postpartum Visits (PP)				FU visit
Beginning of Treatment Week		4 visits over 6 weeks				4.5 months from PP
	BIRTH	PP1	PP2	PP3	PP4	FU
Table 2. Screening Assessment Schedule						
Telephone script & screen (basic eligiblity)						
Informed Consent verbal/signed						
MINI (a)						
Childhood Trauma Questionnaire						
C-SSRS (b)						
TLFB		x	x	x	x	x
FTND						
Smoking History Form						
Medical History						
Urine Test (urine cotinine and/or anabasine collection) - (c)		x	x	x	x	x
Urine pregnancy test (d)						
Concomitant Medications, Other smoking cessation medications_ treatments & other Psychotherapy		x	x	x	x	x (e)
OUTCOME MEASURES						
PHQ-9		x	x	x	x	x
GAD-7		x	x	x	x	x
NICOTINE WITHDRAWAL						
WSWS-28		x	x	x	x	x
MEDIATORS						
PANAS		x	x	x	x	x
PROMIS Cognitive function-abilities		x	x	x	x	x
OTHER						
Counseling		x	x	x	x	
Adverse Events		x	x	x	x	x (e)
Assessment of Changes since last visit		x	x	x	x	x
FEASIBILITY MEASURES						
WAI-Client Short		x		x		
WAI - Therapist		x		x		
Technical issues questionnaire		x	x	x	x	
Acceptability of treatment -		x	x	x	x	x (f)
Acceptability of treatment - Clinician					x (g)	

(a). MINI Modules: (A, C, D, E, F, G, H, K, N, O)
(b). C-SSRS may be done at any visits as clinicially indicated by the Safety Plan
(c). Urine test (cotinine and/or anabasine) will be done at visits where the participant is reporting abstinence and meeting the 7 day point prevalence criteria.
(d). Urine pregnancy test, or if preg test result inconclusive submit paperwork verifying pregnancy
(e). Follow up on any open CCMs/Psychothearpy/Treatments & AEs ONLY
(f). Administer Participant Acceptability of treatment if ppt did not complete at previous timepoints
(g). Clinician Acceptability of treatment may be completed earlier if ppt withdrawals from the study

Request for Waiver of Written Consent We are requesting a waiver of written consent on Aim 1 focus groups, Aims 3 baseline screening visits, Secondary Aim 2 focus groups and study therapist completion of questionnaires and satisfactions ratings. The justification for this waiver request is a) because the research or data collection on each of these study components does not involve procedures for which a written consent is required; b) the verbal scripts contain all of the required elements of a consent and; c) the research conducted during these study components presents no more than minimal risk. For the focus group components, the participants are not MD Anderson patients. The focus group discussion will be conducted virtually with all participants providing verbal consent and completing a screening visit prior to joining the session.

Request for Waiver of Witness to Consent We will request a waiver of witness to consent for all aims involving participants (Aims 1, 3 and 4). All Aims will be conducted virtually; as such, most participants may be in their own homes and may not have another person available to witness the consent. We feel this would place an undue burden on the participant to have to identify and coordinate with a non-study team member as a witness and may prove to be a barrier to participation in the project.
Additionally, this project is looking at soliciting feedback from the target population to assist in the development of counseling treatment manuals; the manuals, in turn, will be used in a small randomized trial to evaluate a depression-focused smoking cessation treatment for pregnant women experiencing depressive symptomatology as assessed by our screening measures. Participants will not be given medications to assist with smoking cessation or mood disorders. Only behavioral interventions will be used, and therefore the project could be considered low-risk.

Provision of Smartphones and Data Plans While the majority of low-income young women own smartphones, only 56% have access to home broadband.[115] To address this potential barrier to data access, we will provide smartphones and unlimited high speed data plans to each of the participants. At this early stage of treatment development, this will allow us to evaluate the feasibility, acceptability and preliminary efficacy of providing BA via videoconferencing. We have negotiated a minimal cost of $25 per month, with free phones provided with this plan. The plans also come with unlimited talk, text and email. Women will be allowed to use the smartphones for personal use. The provision of email addresses and text through the plans will provide another means by which to contact participants. Smartphones will be provided to participants of Aims 1, 3, and 4. For all participants, information regarding the use of video conferencing and completion of questionnaires on the smartphones will be provided at the Pre-Screen assessment visit. Participants will also receive an instruction guide on how to join the zoom video sessions (Appendix. Zoom Participant Instructions). Enrolled Participants in Aims 1, 3, and 4 will be allowed to keep the smartphones and headphones (if they were provided).

Replacement of equipment. Reports of damaged or lost smartphones, and headphones will be reviewed by study staff and a decision made regarding replacements. All efforts will be made to replace equipment one time, with additional requests reviewed by the project supervisor.

Treatment Similar to our previous trial, when women enter the trial later in the gestational age range or miss sessions, we will attempt to schedule two sessions per week and make-up sessions to ensure that women have an opportunity to attend all of the scheduled prenatal and postnatal sessions. Participants will be provided with headphones, if they request them, which

they may choose to use to ensure privacy of therapy session discussions with the therapist. Missed sessions are to be expected and therefore deviations will not be logged.

Participant Withdrawal. A withdrawal occurs when an enrolled participant actively withdraws consent for further participation in the study, prior to completion of the protocol. Participants may withdraw consent from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety reasons. All attempts will be made to conduct all evaluations required by the protocol.

Addressing Negative Birth Outcomes. Preterm and negative birth outcomes are common in low income women, especially those with depression who smoke. We will handle these events in the following manner. Women who do not deliver live births will be allowed to continue postpartum treatment if they wish. We will remove them from the sample and replace them with a new participant. For women who experience preterm birth, we will consider providing additional sessions in the postpartum period to ensure a full treatment dose in these individuals. For women who experience other negative birth outcomes which interfere with participation in the postpartum period, we will attempt to make up for missed sessions by increasing the frequency of sessions within the postpartum treatment timeframe. Should negative birth outcomes cause an imbalance in treatment delivery across treatment conditions, this should be detected in our initial analyses of group differences, which will allow us to treat number of treatment sessions as a confounder if such differences are found to be correlated with outcomes (See Statistical Design and Power, Baysesian Modeling Strategy).

Prenatal.

During the prenatal period, participants of 18-22 weeks gestational age will receive 10 individual sessions of BA or HW. The prenatal HW treatment will be similar to the treatment that was utilized in our previous trial.[51] These women will have 16 weeks to complete their 10 individual sessions.

During the prenatal period, participants of 23-32 weeks gestational age will receive 10 individual sessions of BA or HW. The prenatal HW treatment will be similar to the treatment that was utilized in our previous trial.[51] These women will have 12 weeks to complete their 10 individual sessions.

We may do additional check in calls or text communications with participants to maintain engagement between prenatal and postpartum treatment sessions.

Postpartum. Following birth, women may have up to a month break before resuming individual sessions, though have the option to resume earlier if preferred. Women will receive an additional 4counseling sessions in postpartum over 6 weeks. The participants will complete 1 follow up visit that occurs 4 ½ months postpartum.

Smoking cessation counseling. Smoking cessation counseling will be delivered during the first 15 minutes of the session in both the BA and HW conditions, and will generally follow the Clinical Practice Guideline,[33] providing specific cessation tips and limited social support and problem solving exercises, that will be supplemented with pregnancy focused material relevant to smoking-related topics in the prenatal and postpartum periods. During the postnatal period, smoking cessation counseling will focus on cessation or relapse prevention, depending on the participant's smoking status. All participants will be provided with printed evidence-based pregnancy-specific cessation materials (*Forever Free…For Baby and Me*)[91] that will serve as an outline during smoking cessation counseling discussions (See Section Aims 1-3 Approach 1

(Stage 1A), Focus Group Procedures and Data Analysis for description of postpartum intervention topics.)

BA. Following the 15-minute smoking cessation counseling component, the 45-minute BA component will focus on increasing engagement in rewarding and adaptive activities, decreasing activities such as avoidance and withdrawal that maintain or increase risk for depression, and solving problems that limit access to reinforcers. Behavioral activation strategies include self-monitoring, scheduling daily activities, rating pleasure and accomplishment, exploring alternative behaviors to achieve goals, and role-playing to address behavioral deficits. Postpartum treatment components may be modified depending on the outcome of Aim 2.

HW. Women assigned to HW will receive 45 minutes of didactic health education counseling. They will be told the primary goal of the HW treatment is to educate them on ways to take care of themselves physically during their pregnancies and the postpartum period. The purpose of this condition is to provide a time and attention matched control for BA that is pregnancy and postpartum relevant but instructional in nature. Participants will be allowed to choose from a list of discussion topics including pregnancy symptoms, postpartum hormonal changes, sleep, exercise, breastfeeding, yoga, relaxation training, time management and parenting tips. During the HW sessions, the therapist will review (read and paraphrase) the content contained in the standardized handouts that addressed the chosen topic, noting the connection between the HW topics and smoking, where appropriate. The therapist will be allowed to provide reflective and supportive listening regarding participants' comments on the HW topics and regarding general events raised by participants during the session. The therapist will be prohibited from conducting solution-focused exercises related to HW topics or other problems that participants raise, assigning homework, or initiating discussions of progress made between treatment sessions concerning any of the HW topics that are discussed.

All sessions will be conducted remotely via interactive video conferencing on smartphone devices. All treatment sessions will be videotaped for use in treatment supervision and treatment adherence rating, using an institutionally approved virtual platform (eg. Zoom). Given Dr. Hubley's and other PI designees possible role in supervising the study therapists through viewing of videotaped counseling sessions, as external collaborators they may have access to participants' protected health information during this phase of the study. This has been noted in the consent document for this aim.

At each session, the participant will be asked about any changes to demographics, estimated delivery date, medications, other smoking cessation treatment, other counseling treatment, and health since their last visit (see Appendix: Assessment of Changes since last visit).

Stage IB, Secondary Aim 2 Focus Group Procedures and Data Analysis

During year 3, we will recruit a) women who dropped out of the study during the first month of the postpartum treatment phase, and; b) women who completed at least 3 of the 4postpartum treatment sessions, to participate in 2 focus groups of 6 to 7 women who dropped out and 2 groups of 6 to 7 women who completed treatment. Focus groups will be conducted by teleconference, using participants' study smartphones and teleconference facilities at MD Anderson. Participants will be compensated $75 for completing the focus group sessions. Objectives of Secondary Aim 2 are to collect qualitative data on a) barriers to completing treatment sessions; b) usefulness of postpartum treatment; c) suggestions for decreasing barriers and improving treatment acceptability, and; d) relevant experiences unexpected by participants and researchers. We will use the same procedures to conduct focus groups and

analyze data as described in section Aim 1 (Stage IA). These data will be used to inform further revision of the intervention for evaluation in future trials.

, In the event there are conflicts for participant availability that prevents scheduling a focus group, we will conduct one-on-one interviews with women who meet the eligibility criteria rather than risk losing participants.

Assessment

Remote Assessment Procedures Participants will be assessed for depression, psychiatric disorders, and other measures at baseline, selected measures at each of the prenatal and/or postnatal treatment sessions, and at 4 ½ months postpartum. With the exception of the screening telephone calls prior to enrollment, which will be assessed by telephone or at prenatal clinic visits, data will be directly entered by participants on the smartphone, including daily diaries assessing smoking. Participants will receive SMS or e-mail prompts containing a link at the time assessments are scheduled. Participants who fail to complete assessments as scheduled will receive additional SMS or e-mail prompts and, if necessary, phone call reminders.

Measures

Process Measures and Analysis: AIM 3

Technical issues We will systematically track and assess technical problems with smartphone videoconferencing delivery of treatment, assessment and video recording of treatment sessions. These data will be used to develop items for a measure of frequency and quality of technical difficulties and impact on the treatment session and assessment completion, which will be used in the Stage IB trial (Aim 4). We will also gather information on the effectiveness of contingency plans for completing sessions when interrupted by technical difficulties; and on the level of technical assistance needed to support the videoconferencing and assessment procedures.

Barriers to participation Participants who fail to complete the final treatment session, staff will reach out to participants by phone and/or text to attempt to conduct a telephone interview to assess the degree to which various factors interfered with completion of the treatment and to list reasons they were unable to complete treatment. To encourage completion of these interviews, women will be paid $20. Examples of potential barriers that participants will be asked to rate include lack of childcare, difficulties using the smartphone to complete treatment sessions and assessments, inability to schedule time to complete treatment sessions and assessments, and inability to find locations where sessions could be completed uninterrupted by members of household. We will also administer this interview at the end-of-treatment session (EOT; session 10) to participants who complete treatment and to the study therapists. Participants who complete the EOT session will not receive an additional $20 for this interview as it will be given as a required questionnaire at EOT. Frequencies of each barrier type will be calculated. Eligible participants who decline participation will be asked to provide reasons for declining and frequencies of reasons for declining will be calculated. Based on these data, the investigators will consider whether additional exclusion criteria are needed or whether barriers can be addressed by changing study procedures.

Assessment burden Completion of study measures will be calculated as the percentage of scheduled assessments completed per visit and percentage of scheduled assessments

completed per measure. Participants will be asked to provide feedback regarding their ability to complete the assessments.

Timeline Follow-back Interview (TFBI)[111] Self-reports of smoking will be collected from participants at baseline using the TFBI. Starting at study entry, self-reported smoking will be collected daily with the Ecological Momentary Assessment (EMA) questionnaire(s) sent to the patients phone through the Qualtrics platform, an MD Anderson-approved secure platform for data collection.

Biochemical verification of pregnancy. If the participant is referred directly from UT Health providers, the provider or designee will confirm pregnancy status through their electronic health record prior to the referral. Participants referred by any other means will confirm positive pregnancy status through an at-home test.

Biochemical verification of self-reported abstinence All participants will be asked to complete a urine cotinine test and send a picture of the results to study staff at each visit (beginning with visit 2) when self-reporting abstinence (Aims 3). To provide preliminary evaluation of the feasibility of collecting these data, we will calculate the ratio of received test results to number of participants who completed sessions 2 through 10. We will use a urine cotinine test that measures nicotine at 100 ng/mL, with a negative result to verify abstinence. We will calculate rate of deception based on the ratio of measures meeting this criterion to self-report of abstinence. Point-prevalence abstinence at the end of treatment will be defined as both a self-report of not smoking during the previous 7 days and a negative result.

Adequacy of participant safety procedures We will gather initial data on the effectiveness of participant safety procedures including ability to screen out participants who are inappropriate for remote delivery of treatment due to safety concerns (e.g., suicide risk, severity of psychiatric symptoms) and ability to provide access to local mental health care when needed.

Therapeutic alliance will be assessed using the client rated Working Alliance Inventory (WAI-C), Short Form at V2, V4, V6, V8, and V10. [116] To maintain boundaries in the therapeutic relationship between therapists and the participants with whom they are working, therapists will not be able to access responses or scores on these instruments.

Feasibility Measures: **AIM 4:** We will utilize a participant contact tracking database to document number of participants contacted to discuss participation in the study, number eligible, and number who consent to participate.

Rate of recruitment will be calculated as the percentage of eligible participants who are consented to participate.

Retention will be calculated as the percentage of enrolled participants who complete the 4 ½ month postpartum assessments.

Completion of treatment visits will be documented using the participant tracking database. These data will be used to calculate the average number of treatment sessions that participants attend and percentage of participants who complete the prenatal and postnatal treatment protocols.

Completion of study measures will be calculated as the percentage of scheduled assessments completed per visit and percentage of scheduled assessments completed per measure.

Rate of receipt of other smoking cessation, psychopharmacological or psychotherapeutic treatment following enrollment will be recorded in the database.

The rate of technical difficulty with smartphone delivery of treatment and assessments will be calculated as the percentage of treatment and assessment sessions that are interrupted due to technical difficulties with the smart phone.

Verification of pregnancy. Participants will confirm positive pregnancy status through study provided pregnancy test or provide paperwork verifying pregnancy status if the pregnancy test is inconclusive.

Biochemical verification of self-report abstinence will be calculated as the ratio of received urine test results (cotinine and/or anabasine) to number of participants who self-reported abstinence at 4 ½ months postpartum

Acceptability of treatment will be assessed in both participants and therapists (see table of assessments for AIM 4) for timepoints. Participants and therapists will be asked to provide ratings of their satisfaction with the BA and HW interventions. Areas that will be included in these ratings are number of treatment sessions, timing of treatment sessions, and quality of interaction with therapists and study staff (for participants' ratings) and quality of interaction with participants (for therapists' ratings).

Therapeutic alliance will be assessed using the client and therapist-rated Working Alliance Inventory, Short Form atPN2, PN4, PN6, PN8, PN10, PP1 & PP3 visits. [116] To maintain boundaries in the therapeutic relationship between therapists and the participants with whom they are working, therapists will not be able to access responses or scores on these instruments. In addition, responses on this instrument will be used in data analyses only.

AIM 3 and AIM 4 Assessments:

Baseline characteristics of psychiatric disorders/symptoms and nicotine dependence.

The Mini International Neuropsychiatric Interview (MINI) 7.0.2. [117] The MINI screens for several DSM-5 Axis I diagnoses. Current Major Depressive Disorder, Past or current Bipolar I or II or Otherwise Specified Bipolar and lifetime or current Psychotic disorder will be assessed using specified modules from version 7.0.2 of the MINI.

The Patient Health Questionnaire - Mood Module (PHQ-9). is a 9 item self-report measure used that was developed to assess the participant's mood over the last two weeks and is used for inclusion and also part of the Safety Monitoring Plan

The Columbia Suicide Severity Rating Scale (C-SSRS) is a measure used to identify and assess individuals at risk for suicide. Questions are phrased for use in an interview format but can be completed as a self-report measure if necessary. This is part of the Safety Monitoring Plan.

The General Anxiety Disorder Scale (GAD 7). The GAD-7 is a validated, seven-item scale developed to assess the presence and severity of generalized anxiety disorder symptoms over the last two weeks and is also part of the Safety Monitoring Plan. Empirically-derived cut-offs can be used to quantify severity of reported symptoms.

The Fagerstrom Test for Nicotine Dependence (FTND)[118] is a 6-item scale that will be used to asses nicotine dependence at baseline for Aims 3 and 4.

Biochemical verification of self-reported abstinence Starting after the first treatment session, all participants in AIM 3 will be sent a urine cotinine test at every visit if they self-report abstinence in the last 7 days. In AIM 4, all participants will be sent a urine test (cotinine or anabasine) at every visit is they self-report abstinence in the last 7 days. Participants will be asked to send a picture of the urine test to the research staff via text message or email and/or return the test via mail in the box provided to them. This process is used in several of our

smoking cessation studies and offers the patient a convenient way to provide remote biochemical verification of self-reported abstinence. We will use a urine cotinine test that measures nicotine at 100 ng/mL, with a negative result .

Outcome

Timeline Follow-back Interview (TFBI)*[111]* Self-reports of smoking will be collected from participants *in Aims 3 and 4* at baseline using the TFBI. Starting at study entry, self-reported smoking will be collected daily with the daily diary Ecological momentary assessments (EMA) through the Qualtrics platform. In the event the participant does not complete the EMA daily diary, smoking data will be collected at counseling visits.

Biochemical Abstinence Verification All participants who self-report as being abstinent at each treatment visit will be sent a urine test (cotinine or anabasine)to biochemically verify abstinence. Participants will be asked to send a picture of the urine test to the research staff via text message or email and/or return the urine samples via mail in the labeled box provided to them. This process is used in several of our smoking cessation studies and offers the patient a convenient way to verify smoking and to also provide remote biochemical verification of self-reported abstinence. We will use a urine cotinine test that measures nicotine at 100 ng/mL, with a negative result to verify abstinence. Abstinence Definitions Point-prevalence abstinence at the end of prenatal treatment and end of postpartum treatment and 4 ½ months postpartum follow-ups will be defined as both a self-report of not smoking during the previous 7 days and a negative result. Regarding the primary outcome of abstinence at 4.5 months postpartum, because the study will allow for a variable quit date through the postpartum period, we will consider quit attempts up to week 14 of the postpartum period, which will allow for the recommended 2-week grace period for prolonged abstinence prior to the postpartum end of treatment. Thus, prolonged abstinence at 4.5months postpartum will be defined as a self-report of not smoking from Week 16 through the 4.5-months postpartum follow-up and a negative result .

The PHQ-9[119] will be used to assess depression outcomes. The PHQ-9 has been found to reliably measure response to depression treatment, including responsiveness to criterion standards for full, partial and remission of DSM-IV symptoms of major depression.[120]

The GAD-7 will be used to asses anxiety outcomes. The GAD-7 is a validated, seven-item scale developed to assess the presence and severity of generalized anxiety disorder symptoms over the last two weeks. Empirically-derived cut-offs can be used to quantify severity of reported symptoms.

Treatment Mechanisms

The PANAS[121], a widely-used 10 item self-report measure of the experience of positive and negative affect within the past week, will be used in Secondary Aim 1 exploratory analyses of hypothesized BA mediators (PA and NA). It will be assessed at baseline and each counseling visit.

The PROMIS Cognitive Function-Abilities (CF-A) Short-form[122] is from the Patient Reported Outcomes Measurement Information System. This 8-item scale assesses perceived cognitive deficits, including mental acuity, concentration, memory, and perceived changes in these cognitive functions and the extent to which cognitive impairments interfere with daily

functioning. It will be assessed at baseline and each counseling visit. It will be used in Secondary Aim 1 exploratory analyses of hypothesized BA mediators *(cognitive function)*.

Nicotine Withdrawal

The Wisconsin Smoking Withdrawal Scale (WSWS)[123] This 28 item scale will be used to assess nicotine withdrawal symptoms.

Smoking cessation or depression treatment following enrollment

At each study visit, participants will be asked whether they have started any counseling or medications for the treatment of smoking or depression. These data will be used as covariates in analyses of outcome, as needed.

Additional Measures

Childhood Trauma questionnaire (CTQ). This is a standardized 28-item self-report inventory that measures the severity of five different types of childhood trauma. Approximately 5 minutes is required to complete the questionnaire. A 5-point likert scale is used for the responses from Never true to Very often true.

Medical History. This questionnaire assesses the participants current relevant medical history at the time of the baseline visit.

The Baseline Demographic and Smoking History Form. These questions expand on the data obtained during the pre-screening, providing more detailed information on demographics, information on smoking history (e.g., years smoked, current smoking rate, other nicotine/tobacco use) is also obtained. These questions have been used in our previous and current cessation studies to provide descriptive data for the study population.

Ecological Momentary Assessments (EMA)/Daily Diary. Our EMA methodology is modeled after several of our previous studies in which we enrolled very diverse smoking populations[69,70]. In this study, EMA assessments will be implemented through a Qualtrics link sent to the smartphone provided to the participant. A daily diary assessment will occur only once per day, every day throughout the treatment phase of the study. The participant will be prompted by text message to complete the daily diary EMA assessment and will assess events from the previous day such as cigarettes and other tobacco use. At participant request, EMA links can be sent to the participant's personal phone via SMS message or email address. EMA trainings will be provided to participants as needed. Total time devoted to EMA is fairly reasonable (approximately 5 minutes/day on average), Missed EMA assessments will not be logged as protocol deviations because they are expected in smoking cessation trials.

Measures of Treatment Fidelity

We have included the following recommended procedures[124] for the ongoing assessment of treatment fidelity. To monitor and improve therapist training and delivery of treatment during the Stage IA pilot study, all BA and HW sessions will be videotaped. Two treatment sessions (session 1 and one session randomly selected from sessions 2-5) in both conditions will be rated by Drs. Blalock (PI), Hubley, or a PI designee shortly following the sessions, using BA, HW and smoking cessation rating forms (see Aim 2 Research Design). During the Stage IB trial, all BA and HW sessions will be videotaped, and 20% of randomly chosen sessions will be rated by Dr. Blalock, Hubley, or a PI designee Dr. Blalock or a PI designee will provide regular supervision throughout the Stage IB trial, with guidance from Dr. Hubley. Fifteen percent of the BA and HW sessions that are rated will be rated by a second rater with expertise in the BA or HW smoking cessation interventions. All videotaped sessions will be destroyed within 5 years of completion of treatment fidelity assessment of Aim 4 sessions.

Benchmarks for Establishing Feasibility and Acceptability

A priori benchmarks for feasibility and acceptability will focus on retention at the 4.5-month postpartum assessment and completion of treatment visits. The study will be considered feasible if both the rate of retention at the 4.5-month postpartum assessment and average percentage of completed treatment sessions across subjects are 70% or above unless, in the case either rate is lower than 70%, we have convincing arguments that they can be improved sufficiently by modifying recruitment or intervention strategies. We will calculate statistics to estimate these feasibility parameters and calculate their 90% confidence intervals (CI), based on our sample size.

Adverse Event Monitoring & Concomitant Medication.

Adverse events and concomitant medications will be assessed throughout the study. Our procedures for assessing adverse events follow standard FDA and clinical practice guidelines and are well established in our research programs. Adverse event (AE) terminology and grades will be determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, published by the U.S. Department of Health and Human Services. Only psychiatric adverse events, whether or not related to the treatment, will be reported. The counseling component will be overseen by PI Dr. Blalock.

Adverse events will be reviewed by the PI and further reviewed by the medical team when appropriate. Adverse event monitoring will stop at the final treatment visit, or earlier if the ppt withdraws or becomes lost to follow up. Those AEs that are probably, possibly or definitely related to the treatment will be followed until resolution or end of study, whichever comes first. In the case of reports of suicidal ideation, depression or anxiety which we believe may be related to treatment, if possible, we will engage in our normal psychological assessments. This may not always be possible if reported by phone. In any case, procedures for Good Clinical Practice will be followed with respect to medical management of the symptoms. A specific plan for monitoring increased depression, anxiety, and suicidality is presented (Appendix. C-SSRS). The clinical assessment tools we use are the PHQ 9, GAD 7, and C-SSRS. The procedures are outlined (Appendix. Safety Monitoring Plan) apply to both symptoms of anxiety, depression, and suicidality. Treatment- emergent psychosis is extremely rare in smoking cessation trials. If it does occur, it will be captured by our assessment of adverse events. These cases will be referred for further evaluation by a Ph.D. Clinical Psychologist. The PI is responsible for determining the attribution of adverse events to the treatment.

Serious Adverse Event Reporting (SAE) Reporting

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

• Death
• A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
• Inpatient hospitalization or prolongation of existing hospitalization
• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
• A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
• Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator.
• All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".
• Serious adverse events will be captured from the time of the first protocol-specific intervention, until the last treatment visit, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

STATISTICAL DESIGN AND POWER

We will employ a randomized, controlled between groups design in which 60 depressed pregnant smokers will be randomly assigned, using a form of adaptive randomization called minimization, to either Behavioral Activation (BA) or Health and Wellness (HW). We will stratify treatment assignment by baseline depression, smoking rate, and gestational age.

Data analyses will be conducted by our University of Texas Health Science Center collaborator Charles Green, Ph.D. Dr. Green will be provided deidentified data from which to conduct the analyses and thus will not have access to participants' protected health information (PHI).

General Data Analytic Strategy: Bayesian Statistical Methods

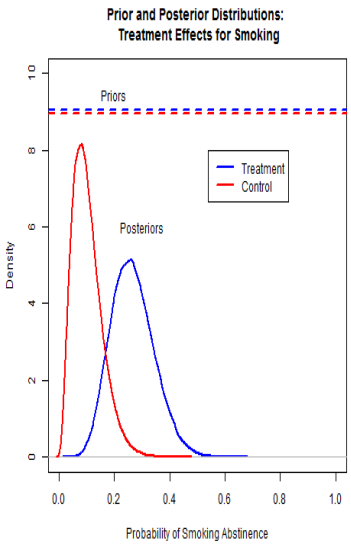
Developing effective behavioral interventions requires incremental improvement of theoretically sound treatments based on systematically accruing data. Often this incremental development is hampered by statistical tools not appropriate to the task. Classical, Frequentist statistics have advanced the science of behavioral interventions substantially but are less informative for the initial test of a new treatment. The reliance of the Frequentist framework on dichotomous, null hypothesis-testing provides some control of the error rate in the context of multiple repeated trials; however, this is not what early-phase treatment testing requires. Developing nascent treatments requires investigators to bet on an alternative hypothesis. Investigators evaluating a theoretically sound intervention want to know the probability that the approach confers some level of benefit given the observed data: that is, they want to know the probability that the alternative hypothesis is true. While Frequentist inference does not directly address this issue, Bayesian statistical inference provides a principled approach to answer this question. Indeed, addressing the so-called "Pipeline Problem" in developing clinical applications, the FDA has indicated that Bayesian statistics offers one avenue for improved

methodological efficiency.[125–130] Decision-making based on an initial trial of a treatment is assisted by estimates of the probability of an effect of some specified magnitude. These statements, not part of the conventional, Frequentist statistical lexicon, are accessible via Bayesian approaches, particularly with small sample sizes.[131, 132]

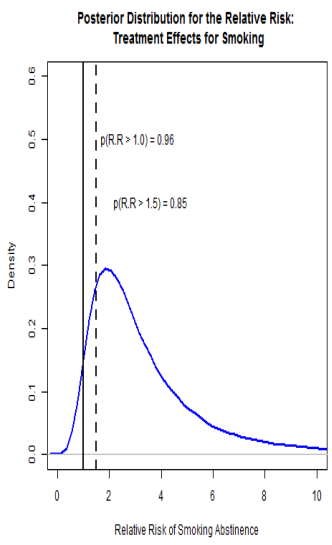
Detailed descriptions of Bayesian statistical reasoning exist elsewhere.[133–135] Succinctly, Frequentist models estimate the probability of observing the data (or data more extreme) given that the null hypothesis is true; Bayesian analyses estimate the probability of the alternative hypothesis given the observed data.[135] Bayesian probability estimates incorporate prior information about plausible parameter values (i.e., the prior distribution) and the observed data (i.e., the likelihood). Combining these two distributions forms the posterior distribution which permits evaluation of the probability that the true value of the parameter falls in some range.

Simulated Example: As an example of applying a Bayesian analysis, the Figure below depicts the prior and posterior distributions for the probability, and the posterior distribution of the relative risk of smoking abstinence as a function of intervention ***based on simulated data***. Panel A shows the prior and posterior distributions of the absolute probability of treatment initiation as a function of the intervention. The prior distributions (dashed lines) assume that for both intervention conditions all probabilities of smoking abstinence are equally likely (i.e., ~Beta[a=1, b=1]). The posterior distributions (solid lines) reflect anticipated intervention effects:

Panel A



Panel B



1) N= 60 participants randomized in a 1:1 ratio, **2)** 7.6% and 25% rates of abstinence at six months post-partum in the control and intervention conditions, respectively (i.e., ~Beta[a=3.28, b=28.72] and ~Beta[a=8.5, b=23.5] for control and intervention conditions, respectively). Panel B reflects the posterior distribution of the relative risk (calculated directly from the distributions in Panel A (i.e. p(Abstinence in Intervention)/p(Abstinence in Control)) for smoking abstinence. From a Frequentist perspective, this would yield a Fisher Exact p $\leq$ 0.18 and relative risk of 2.67 (95% CI 0.78-9.09). (Note: For the Frequentist calculations, to address the non-integer nature of the estimated frequencies, coupled with the low numbers in the control condition we chose to round any fraction for abstinence upward. This had the effect of producing a slightly higher effect in the control condition (n = 3 versus n = 2 abstinent) therefore rendering the simulated effect size more conservative). A fundamental difficulty is that the Frequentist approach cannot provide any indication regarding the relative probability of different values within the 95% Confidence Interval being the true parameter. The Bayesian estimate of the relative risk is slightly different (rounding was necessary in estimating the Frequentist but not the Bayesian solution), RR = 2.73, (95% CI: 0.90-11.44), however since these estimates are based on a posterior distribution it is possible to discuss the probability that an effect of a given magnitude is the governing parameter. Defining benefit as any RR > 1, the simulated posterior distribution shows that there is a 96% chance that the intervention confers this benefit and a more stringent definition (Relative Risk $\geq$ 1.50) is associated with an 85% probability that intervention confers

benefit. We stipulate that an intervention effect that has at least a 75% probability of increasing the relative risk of abstinence by >1.25 will warrant further investigation in a larger trial. While the above simulation provides a straight-forward example of how Bayesian modeling works, it is often necessary to use more sophisticated Bayesian approaches (e.g., logistic regression with Monte Carlo Markov Chain estimation methods). As such, final analyses will utilize Bayesian generalized linear modeling with multilevel-modeling for repeated measures data.

Bayesian Modeling Strategy Initial analyses examining group differences for baseline variables will use cross-tabulation, ANOVA's, and examination of correlations between baseline variables and specified outcomes. For the purposes of evaluating the comparability of groups, a posterior probability of ≥ 95% will constitute evidence for statistically reliable differences. Baseline or demographic variables on which group differences are detected, and which are correlated with outcomes, meet the definition of confounders[136, 137] and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will permit determination of the degree to which any group differences might confound conclusions regarding treatment.

Broadly, the data analytic strategy will use generalized linear and multilevel models (SAS 9.4, R v. 3.5, and Stan 2.17) for both discrete (e.g. smoking abstinence) and continuous (e.g. depression) outcomes.[138–140] Cross-sectional continuous (depression), dichotomous (smoking abstinence) and time-to-event (retention) data will be evaluated using generalized linear modeling or proportional hazards regression. All analyses will apply intention-to-treat principles with missing imputed as non-abstinent for smoking outcomes. For outcomes other than smoking, Bayesian approaches will implement joint modeling of observed outcomes and the missing data which is robust to ignorable missingness (i.e., MCAR and MAR).[141] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.[142] Convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will be assessed via graphical (Trace Plot, Autocorrelation Plot) and quantitative (Gelman-Rubin Diagnostics and Effective Sample Size) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear models, priors for regression coefficients will be specified as ~Normal ($\mu=0$, $\sigma^2=1 \times 10^4$), level one error variances will be specified as ~Half-Normal ($\mu=0$, $\sigma^2=1 \times 10^4$). Choice of prior distribution for level two variances will follow Gelman's recommendations.[143] Bayesian Structural Equation Modeling (**BSEM**) prior specification will adapt recommendations from Muthén and Asparouhov.[144] Priors for the comparison of proportions will be specified as ~Beta ($\alpha=1.0$, $\beta=1.0$).

Mediational modeling will examine the degree to which putative mechanisms of behavioral change transmit the effects of the intervention on the specified outcomes. BSEM will investigate mediation of treatment effects by hypothesized mechanisms (positive and negative affect and cognitive deficits) utilizing MPlus v. 8.0.[144–146] Measurement of positive and negative affect will use the PANAS. Measurement of cognitive deficits will use the CF-A. Models will evaluate whether change over time (captured using growth factors) in positive affect, negative affect and cognitive deficits, measured with the PANAS and CF-A, mediates the effect of treatment at six months post-partum. Examination of the posterior distribution of the indirect effects will evaluate the probability that mediational effects exist. For model simplicity it may be necessary to break these analyses into two distinct mediation models. However MCMC estimation has demonstrated superior small sample performance relative to maximum likelihood-based approaches in continuous, normally distributed data.[147, 148] As discussed in the **Specific Data Analytic** section, minimal variability in growth factors representing change over

time, which may be partially a function of small sample size will result in use of an alternative approach.

Specific Data Analyses: Aim 4
The specific quantitative, analytic plan will focus on Primary Aim 4 and Secondary Aim 1.
Primary Aims

Aim 4 (Stage IB)

Conduct a preliminary randomized trial with depressed pregnant smokers comparing the BA to HW to evaluate the following: 1) The effect of BA on abstinence at 4 ½ months postpartum, which is a primary outcome. Logistic modeling will evaluate smoking abstinence, measured by biochemically verified TLFB, at 4 ½ months postpartum as a function of treatment group. **2) The effect of BA on depression at 4 ½ months postpartum, which is a primary outcome.** Generalized linear modeling will evaluate depression, measured by the PHQ-9, at 4 ½ months postpartum as a function of treatment group. **3) Feasibility of depressed pregnant smokers' acceptance of the smartphone delivery of BA and HW, and assessment components indicated by a) retention, which is a primary outcome, b) completion of prenatal and postpartum sessions, which is a primary outcome c) completion of study assessments, which is a secondary outcome d) strength of therapeutic alliance from both the participant and therapist perspective, which is a secondary outcome and e) participant and therapist ratings on satisfaction questionnaire, which is a secondary outcome.** Survival analysis will evaluate retention by modeling time to drop-out as a function of treatment condition. Binomial logistic modeling will evaluate the proportion of completed sessions as a function of treatment condition across the entire study as well as in the pre-natal and post-partum periods separately. Generalized linear models will evaluate participant and clinician measures of therapeutic alliance, measured by the WAI, as a function of treatment group. Similarly, generalized linear modeling will evaluate satisfaction as a function of treatment group. **4) Feasibility of study procedures as indicated by a) percentage of sessions interrupted by technical difficulties, which is a secondary outcome, and b) percentage of urine tests (cotinine and/or anabasine) received for biochemical verification of self-reported abstinence at 4 ½ months postpartum follow-up, which is a secondary outcome.** Binomial logistic models will evaluate the proportion of sessions interrupted for technical difficulties and the proportion of biochemically verified abstinence measures as a function of treatment. These analyses will provide estimates with 95% credible intervals for each of these proportions in each group that will permit assessment of feasibility.

Specific Analyses: Secondary Aim 1 (Stage IB)
Evaluate change in hypothesized treatment mechanisms including positive affect, negative affect and cognitive impairment in relation to treatment effects on smoking and depression. It would be ideal to evaluate the change in positive affect, negative affect and cognitive impairment as mediators of treatment effects on 4 ½ month post-partum outcomes via structural equation modeling. Specifically, we could model the change over time in each mediator and evaluate the degree to which each growth factor might transmit the effect of treatment. However, it is possible that a sample size of N = 50 will not provide enough variability to estimate certain parameters implied by such a model (e.g. the slope of change in each of these mediators may have minimal variance and function poorly as a mediator). If this latter scenario obtains, we will evaluate each component of a mediational analysis in separate analyses to evaluate the evidence for mediation of treatment effects by positive affect, negative affect and cognitive impairment. Specifically we will: a) evaluate the change over time in each mediator as a function of treatment using multi-level modeling; b) Evaluate the effect of

treatment on the outcome (smoking cessation or depression); and c) evaluate the outcome (smoking cessation or depression) as a function of change in the mediator captured either through a difference score (six months – baseline) or residual change score (six months residualized on baseline. While the former (SEM) approach would provide a more elegant test of the overall model of behavior change, the latter may be necessary based on the properties of the sample.

PARTICIPANT SAFETY MONITORING PLAN

Assessment of Worsening Depression, Anxiety and Suicide Risk

As outlined in the Safety Monitoring Protocol and Procedures (see Appendix), we will evaluating and assessing the severity of depressive and anxiety symptoms, other psychiatric disorders as well as suicide risk, using information from the PHQ-9, C-SSRS, and MINI administered at screening (AIM 1), and the PHQ-9, C-SSRS, MINI and and Generalized Anxiety Disorder – 7 (GAD-7), administered at screening (AIM 3 & Aim 4). Additionally, we will be assessing for depressive and anxiety symptoms and suicide risk at the counseling sessions throughout treatment and have outlined procedures for monitoring changes of these symptoms and ideations (Appendix Safety Monitoring Plan). The document also outlines procedures for addressing other mental health concerns, reporting of elder or child abuse and neglect, domestic/intimate partner violence and crises that occur during sessions.

Participants who are rated on the Columbia-Suicide Severity Rating Scale at screening as having active suicidal ideation with some intent to act and active suicidal ideation with specific plan and intent, who fall within the extremely severe range of depressive symptom severity, who endorse having severe vegetative symptoms, bipolar symptoms, psychotic symptoms, or who are experiencing symptoms associated with Axis I disorders that place them at risk of harm will be further evaluated by a designated Master's or Ph.D. level Mental Health Professional (MHP) to make an appropriate treatment disposition. When needed, participants will be referred to collaborators at The University of Texas Health Science Center (UTH) to manage the action plan/treatment interventions as they deem appropriate or provided with outside referral(s).

Vulnerable Subjects

There is no additional risk to pregnant women and their fetuses posed by participation in the study. The intervention seeks to reduce smoking and depression in women in both the prenatal and postpartum period. Reduction in smoking and depression during these periods may benefit both the woman, the fetus and the neonate.

Procedures to protect confidentiality include: 1) Study participation will be confidential and not included in participants' medical records. 2) Confidentiality will be protected by identifying all subjects by ID numbers only with their names kept within a MD Anderson approved secure web-based applications and institutionally approved databases (see Data management, Quality, and Security section). 3) Participants will not be identified in any public reports or documents. Only the PI and data manager have access to the master file linking ID and other data to participant names. All information will be reported in aggregate form and individual participants will not be identified in any public reports or documents. We expect these procedures to be highly effective for protecting participant confidentiality.

Information collected during participation in the study will be kept confidential. In order to protect the participant's information, we received a NIDA (National Institute on Drug Abuse) Certificate of Confidentiality. We will treat all responses confidential to the extent possible. We will follow the HIPAA rules as mandated by MD Anderson and NIDA.

DATA MANAGEMENT, QUALITY & SECURITY

As part of the ongoing monitoring of the project, study investigators and staff are responsible for ensuring that data quality assurance procedures are developed and maintained. Several procedures will be used to maintain the integrity of the data.

REDCap For AIM 1, process measures, participant contact and clinical progress notes will be collected and managed using REDCap (Research Electronic Data Capture, www.project-redcap.org) electronic data capture tools hosted at MD Anderson. REDCap is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (August 2016) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

Trained data collectors will use the databases uploaded to or enter directly into the MD Anderson REDCap system. Automated prompts may facilitate some participant contact and treatment delivery activities. MD Anderson's Research Information Systems and Technology Services (RISTS) group provides deployment and integration support for research data management using the REDCap (Research Electronic Data Capture; www.project-redcap.org) application.[149] REDCap (https://redcap.mdanderson.org) allows researchers and program directors at MD Anderson to create projects with data collection instruments and share those projects with colleagues. Researchers and program directors can capture and analyze data through a simple web-based interface. REDCap is a two-tier pHp-based web application that can be hosted on a variety of hardware and operation systems.

For AIMs 3 & 4, all data will be stored in the institutionally approved Tobacco Research and Treatment Program (TRTP) database (APPID-264846) in a centralized location on institutional servers behind the firewall, which is backed up daily, with access limited to specific users at the discretion of the PI. The PI will assure that audits of selected subsets of data are performed and that appropriate safeguards of participant privacy are maintained. Privacy safeguards will include appropriate password protection and physical security for all computer systems.

Additional quality assurance procedures include a data collection protocol documented in a procedure manual; and regular meetings between the study statistician, the PI, data managers, and other project staff to review problems and solutions, and discuss concerns. Data entry systems, whether via Qualtrics or hand entry with verification, specifically provide field checks, range checks for continuous variables and valid value checks for categorical variables; checks for legitimate dates and times and logical consistency. During data collection, we will

issue reports weekly, or even following any new data entry, depending on the needs of the project. Queries and reports will be provided to the PI. Preliminary review will be initiated shortly after data collection begins to allow monitoring of data quality.

Videoconferencing Software We will work with MD Anderson Infosecurity to identify a HIPAA compliant videoconferencing software package through which to deliver the treatment sessions.

Focus Group Protected Health Information Data and identifiers from focus group audiotaped interviews will be stored behind the institutional firewall on encrypted servers with restricted access only to study team members and will not be reused or disclosed to any other person or entity (except where required by law), or for other research, without prior approval from the IRB. Electronic data and identifiers will be retained indefinitely on MD Anderson servers behind the institutional firewall and will be archived per institutional standards.

Data Storage Participants' names and identifiers will be linked to the project identification number in databases—located on MD Anderson servers behind institutional firewalls—that will be password protected, with access restricted to the project staff, Principal Investigator and study collaborators. Electronic data and identifiers will be retained indefinitely on MD Anderson servers behind the institutional firewall and will be archived per institutional standards. Paper records will be kept in a locked file room. Names will not be identified in any reports resulting from the study, and no individual information will be released to anyone outside of the study. Data will be secured in password-protected computer files and reported at the group level. Data will not be destroyed and will be archived per institutional standards.

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