Reductions in Biopsychosocial Risks for Pregnant Latinas and Their Infants: The Mastery Lifestyle Intervention

Protocol Number: NA First Submission

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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8 PROTOCOL SUMMARY

8.1 SYNOPSIS

Title: Reductions in Biopsychosocial Risks for Pregnant Latinas and Their Infants: The Mastery Lifestyle Intervention

Grant Number: ***R01 HD101535-01A1***

Study Description: To address the gaps related to interventions for Hispanic Mexican American pregnant women, we have developed and successfully pilot tested the Mastery Lifestyle Intervention **(MLI**): a culturally-relevant, manualized psychosocial group intervention that integrates two evidence-based behavioral therapies – Acceptance and Commitment Therapy (ACT) and Problem-Solving Therapy (PST). The MLI is a 6-week program designed to be integrated into regular prenatal care to facilitate more comprehensive care delivered by a nurse practitioner (NP) or certified nurse midwife (CNM). We propose the following hypotheses for a randomized controlled trial: **Hypothesis 1a:** Participants in the 6-week MLI will have decreased depressive symptoms, anxiety, stress, disengaged coping, and increased active coping compared to UC at end-of-treatment and after 6 weeks. **Hypothesis 1b:** The effects of MLI versus UC on depression, anxiety, stress, acculturative stress, and coping will be mediated via psychological flexibility and moderated by acculturation. **Hypothesis 2a:** Compared to UC, MLI participants will have significantly lower mean levels of CRH over time from baseline to end-of-treatment. **Hypothesis 2b**: Compared to UC, MLI participants will have significantly higher progesterone levels and lower estriol levels (higher progesterone/estriol ratios) over time from baseline to end-of-treatment. **Hypothesis 3:** As compared to UC, infants from mothers in the MLI group will have longer gestational age, greater birth weight, and fewer NICU admissions.

Objectives*: **Primary Aim 1:** Determine the efficacy of the MLI in pregnant Latina women to decrease depressive symptoms, anxiety, perceived and acculturative stress, and to improve coping, versus usual care **(UC),** from baseline (14-20 weeks' gestation) to end-of-treatment (20-26 weeks' gestation) and at a 6-week follow-up (26-32 weeks' gestation), with acculturation as a moderator and psychological flexibility as a mediator. **Exploratory Aim 2:** Explore the effect of the MLI on neuroendocrine risk factors of PTB (CRH, progesterone, and estriol) versus UC from baseline to end-of treatment. **Exploratory Aim 3**: Explore the effect of the MLI on infant birth outcomes (gestational age, birthweight, NICU admission.

Endpoints:	The primary endpoints are depressive symptoms, anxiety, perceived and acculturative stress, and coping at 20-26 weeks and 26-32 weeks' gestation of pregnancy, and the secondary endpoints are blood levels of CRH, progesterone and estriol as well as infant outcomes at delivery.
Study Population:	The population of interest is Latinas of Mexican heritage living in the Houston metropolitan area. Our target sample is 234 pregnant women; we will over recruit up to 351 women over ~ 4 ½ years, allowing for a 15% attrition rate. Ages of pregnant women will be between 18 and 45 years; participants will need to identify as a Latina of Mexican heritage. They will need to be in good health without systemic infections. The geographic area is the Houston metropolitan area, including outlying areas that the Texas Medical Center serves.
Phase or Stage:	This is a phase 2 study
Description of Sites/Facilities Enrolling Participants:	All participants will be enrolled from Dr. Anthony Chavez' practice in the Texas Medical Center in Houston. The site sees ~40 new pregnant women monthly, of whom 80% are less than 10 weeks' gestation or 32 eligible women monthly, yielding 16 eligible women monthly. Dr. Chavez serves many pregnant women who are ensured by Medicaid.
Description of Study Intervention/Experimental Manipulation:	We will hold six weekly sessions of the study intervention (the Mastery Lifestyle Intervention, MLI) starting at 14-20 weeks' gestation to 20-26 weeks' gestation with each session lasting ~1-1½ hours. We will give participants in the MLI group a participant handbook in either English or Spanish that has space for reflection and activities to complete at home. We have refined our facilitator handbooks extensively. Conducting the MLI with groups is feasible, acceptable, and advantageous as it is a) cost-effective, b) allows for group support and building a social network (important to Latinas) and c) encourages good role modeling. A recent meta-analysis found no significant differences in effectiveness in individual versus group formats for CBT. If the COVID-19 epidemic continues to require limited face-to-face contact, we will use a web-based format such as Zoom over the phone.
Study Duration:	The study should take 51 months from first enrollment to completion of data collection.

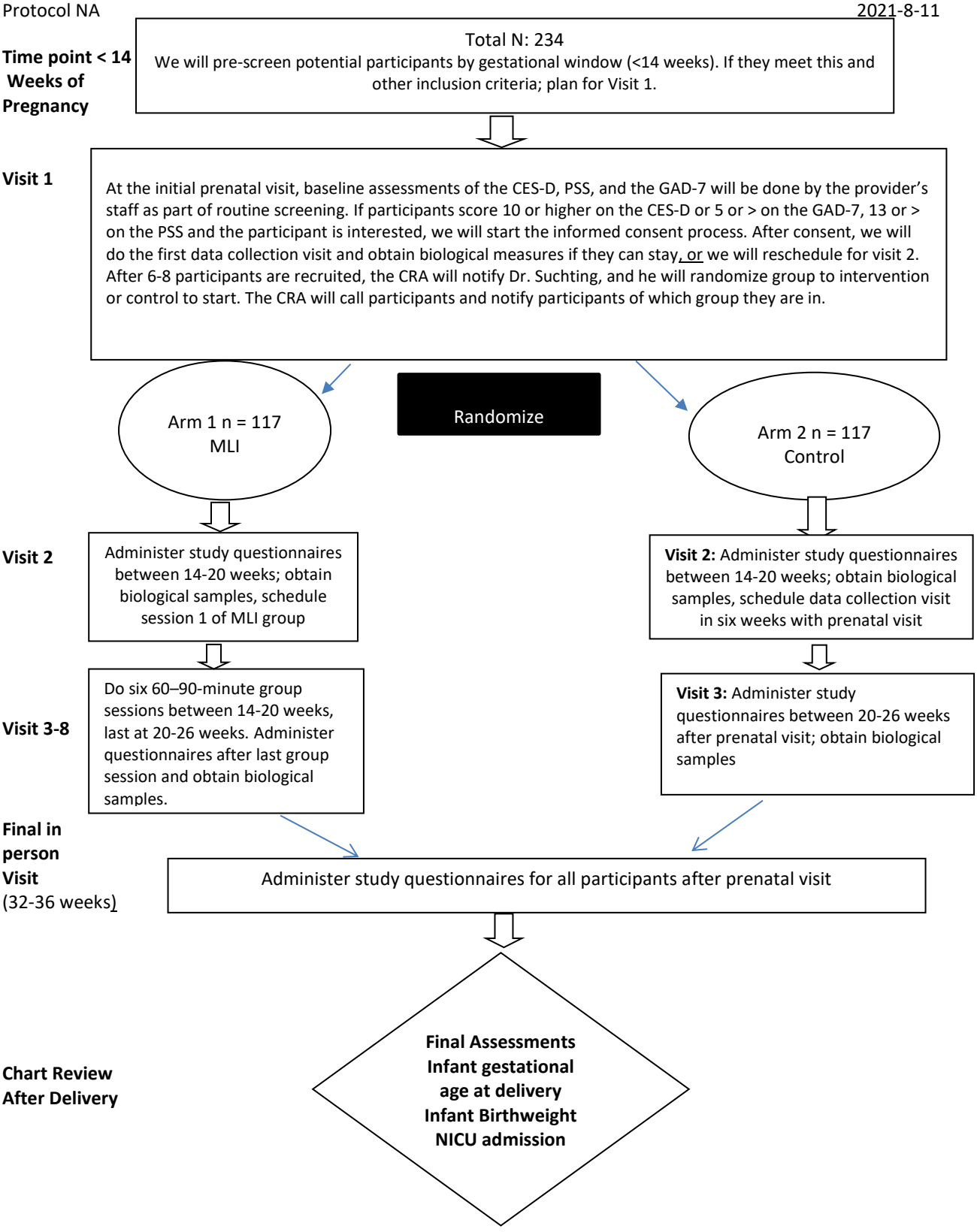
Participant Duration: Each individual participant will take 12 weeks for complete maternal data collection. Data about infants born to participants will be collected via chart review at delivery hospitals.

8.2 SCHEMA (SEE NEXT PAGE)

Reductions in Biopsychosocial Risks for Pregnant Latinas and Their Infants: The Mastery Lifestyle Intervention

Version 2

Protocol NA 2021-8-11



Based on NIH Protocol Template for Behavioral and Social Sciences Research

8.2 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Initial Enrollment in the study	Visit 2 If data not collected at Visit 1	Visit 3 1 week later MLI group only)	Visit 4 1 week later	Visit 5 1 week later	Visit 6 1 week later	Visit 7 1 week later	Visit 8 (20-26 weeks) Final in person visit 32-36 wk Delivery
EMR Review Eligibility	X								
Review scores on PHQ-9, GAD-7 and eligibility	x								
Informed Consent		X							
Demographics		X							
Clinical and prenatal history		X							x
Height & Weight		X							
Questionnaires		X	x		x				x
Obtain biological samples		X	x						x
Randomization of groups after 6-8 women are enrolled		x	x						
Experimental Intervention (MLI) group		x	X	X	X	X	X	X	x x
Usual care group (UCG)		x	x						x x
Collection of Infant Outcome Data Both groups									x
MPFI Questionnaire MLI Group		x	x		X				x x
Adverse Events Reporting		X	X	X	X	X	X	X	x x

9 INTRODUCTION

Background and Significance for Clinical Trial

Psychosocial distress (depression, anxiety, chronic stress, acculturative stress) is prevalent in pregnant Mexican American Hispanics (hereafter referred to as Latinas) and is associated with preterm birth (PTB) and low birth weight (LBW). PTB in 2017 for all births rose (9.93%), rising in Latinas to 9.61% (1**).** Depressive symptoms, anxiety, perceived, and acculturative stress, and deleterious coping are important risk factors related to these results. About 10-25% of pregnant women in the U.S. have depressive symptoms, with resulting negative sequelae for women, children, and families (2). Antenatal depression, a strong risk factor for postpartum depression, highlights the need to intervene early during pregnancy (3). Although postpartum depression is outside the scope of study, we will examine it in future studies, and we will examine the effect of untreated antenatal depression on infant outcomes at birth (LBW, PTB). A meta-analysis found that pregnant women with untreated depression had an odds ratio of 1.56 (1.25-1.94) for PTB and 1.96 (1.24-3.10) for LBW (2). Most evidence indicates that there are ethnic disparities in antenatal depression; Latinas have higher risk factors for depression as compared to non-Hispanic white women (2), with rates of depression as high as 35-40%. In our previous study with Latinas (Ruiz-R01NR07891), 30% had antenatal depression. The prevalence of depression and accompanying psychosocial distress, particularly among impoverished women, is a significant public health problem. Anxiety commonly co-occurs with depression as many as 60% of women diagnosed with depression also met diagnostic criteria for anxiety (5). Similarly, perceived stress is another well-established risk factor for antenatal depression (6) that affects PTB (7-10). Of concern, studies of antenatal depression in Latinas failed to account for acculturation, the multidimensional process of psychological and cultural change that occurs when a person interacts with two or more cultures (11). Previous results for ours and other's studies indicate that greater acculturation results in worsened mental health (12, 13); it is important to consider acculturation as a mediating risk factor for Latinas. Acculturative stress, the stress associated with acculturation, also relates to anxiety and depression. We will examine acculturation and acculturative stress as part of the social risks for poor mental health and birth outcomes. We will avoid methodological weaknesses by focusing on Latinas of Mexican origin, avoiding heterogeneity (14). We will not ascertain if a participant has a social security number, as doing so was noted as a human subject concern by reviewers.

Psychosocial factors increase the risk of adverse birth outcomes.

Depressive Symptoms and Anxiety. Evidence from several meta-analyses (16-18) indicates that the use of antidepressant medications (particularly Selective Serotonin Reuptake Inhibitors [SSRIs]) is possibly related to increased risk of PTB as well as LBW. These findings underscore the need to weigh the effect of untreated depression against the potential effects of antidepressant exposure, (18) and to identify and implement effective nonpharmacological treatments. Treating depression during pregnancy for low-income women can be difficult due to limited insurance coverage for mental health and out of pocket costs, (19) as well as the stigma associated with mental health visits. Depression is often comorbid with anxiety; together, they increase the risk for PTB (20). Several researchers have found strong links between anxiety and PTB (21). There is also evidence that maternal prenatal anxiety programs the fetus resulting in emotional and behavioral problems for the child (21-23). *Based on the evidence related to risk, we will target depression and anxiety to reduce psychosocial risk, ultimately reducing the risk of adverse birth outcomes.*

Chronic Stress. Perceived stress has been extensively studied in relationship to PTB, with strong empirical evidence indicating links between prenatal stress and PTB (7,8). However, acculturative stress and perceived stress together have the greatest impact on elevated depressive symptoms in Latinas (24).

Acculturative Stress refers to stress responses by immigrants culturally adjusting to a new society as they are challenged by an unknown culture and differing social norms. Acculturation involves embracing new behaviors and customs while either preserving or losing those of the traditional culture. Often acculturation and acculturation stress result in intergenerational family conflict, maladjustment, and marginalization (25, 26). Most recently, acculturative stress for Latinas may be exacerbated given the recent increase in sociopolitical stressors (e.g., anti-immigrant, anti-Hispanic policies, hate crimes). Although evidence on the health effects of anti-immigration rhetoric and policies is still being collected currently, studies have related sociopolitical stress (i.e., anxiety about deportation, awareness of anti-immigration policies) with poorer mental health (27) as well as higher systolic blood pressure and pulse pressure among Latina adults, known risk factors for PTB (28). Documented increases in heightened profiling and deportation may not only result in increased acculturative stress but also decreased healthcare use (27). For instance, in a study using birth certificate data, severe sociopolitical stressors among Latinas indicated a detrimental impact on PTB (29). This study illustrated the implications of racial stressors for increased PTB in both the health of Latina immigrants as well as U.S. born Latinas. Rates of LBW and PTB also increased in Latina mothers in Iowa after a surprise immigration raid (30). Further, LBW risks in this study were worse for mothers with low education, who had fewer coping resources. Investigators speculated that the pregnant Latinas' neuroendocrine balance and coping resources were affected after the raid, leaving their infants vulnerable to a dysregulated endocrine environment. Previous scientists found acculturative stress to be a major contributor to poor health outcomes (31,32), but more work is needed to understand the role of maternal mental health. Our last major study with Latinas (Ruiz-R01NR07891) found acculturative stress (as measured by the Acculturative Stress Scale) (33) to be significantly associated with depression (r = .21, p < .000) and chronic stress (r = .24, p <.000*)*, as measured by the Perceived Stress Scale (34). *Both types of stress are proposed targets to reduce psychosocial risk*.

Coping. Poor coping skills, such as disengaged coping, may also be associated with compromised mental health and risk of poor birth outcomes. Disengaged coping may be conceptually defined as avoidance, behavioral disengagement, or self-blame. Relations between coping and antenatal depression among Latinas remain minimally explored; however, among Latinos in general, Torres found among 148 adults, poor coping was associated with worsened depression (35). Of further concern, Borders, studying 294 welfare recipients, found poor coping skills (avoidant or disengaged coping) were associated with LBW babies (36). In general, pregnant women with coping behaviors of avoidance or distancing (i.e., behavioral disengagement) have had more PTB and postpartum depression (36-39). Alternatively, active coping may be conceptually defined as the use of emotional and instrumental support, use of humor, and/or acceptance (vs. avoidance) of internal distress (40). Ours and other's evidence indicate that first-generation Latinas used less active coping skills than acculturated Latinas (41,42). *We will focus on increasing acceptance of difficult internal states (i.e., depression, anxiety) and the use of more action-oriented (vs. avoidant coping) to reduce psychosocial risks.*

Neuroendocrine factors are important for the maternal-fetal response to psychological distress. Research has demonstrated that neuroendocrine pathways mediate the effects of

psychosocial factors on health outcomes, i.e., particularly fetal development and infant birth outcomes (43). In seminal work, Chrousos (44) linked the neuroendocrine system to the stress response and health outcomes. The hypothalamic-pituitary-adrenal **(HPA)** axis (in pregnancy, the placental-pituitary-adrenal-axis) is one of the major systems involved with the stress response. The main agent of this axis is Corticotropin Releasing Hormone **(CRH);** placental CRH is identical to hypothalamic CRH both biologically and in its response to stress (45). Wadhwa (46,47) states that the placenta has the ability to receive, process, and respond to certain stimuli, and thus may take on functions similar to the central nervous system in the stress response. Placental CRH facilitates the placenta getting information to the fetus. Increases of CRH early in pregnancy have predicted the onset of preterm labor in ours and other's results (48-52). The chronicity of stress is particularly important in relation to the initiation of early labor (53). Estrogen and progesterone are other important endocrine factors linked to CRH and related to labor. Increases in estrogen (estriol, **E3)** and decreases in progesterone shift the endocrine balance. Placental CRH stimulates E3 induced changes in the cervix and uterus, part of the initiation of labor (54). It is important to explore the effects of an intervention to reduce psychosocial distress on some of the key pathways, such as CRH, progesterone, and estriol. In our previous study with Latinas (55), the combination of acculturation, depressive symptoms, progesterone, and E3 predicted PTB, indicating that the combined impact of these factors produced the greatest risk. *We propose to a) test a behavioral intervention to reduce psychosocial risks, and b) explore the impact on neuroendocrine factors and infant birth outcomes.*

Cognitive behavioral therapy (CBT) is recommended for reducing antenatal depression, yet effects are small, and few studies have targeted PTB or Latinas. In a recent evidence report of interventions to prevent perinatal depression by the U.S. Preventive Task Force (USPSTF) (56), counseling interventions, primarily CBT, were recommended to prevent perinatal depression. Fifteen of the 20 trials reviewed had counseling interventions that were focused on women who were known to be at risk for perinatal depression, particularly depression history or symptoms. Analysis of counseling interventions revealed a pooled standardized effect size of 0.2, considered a small effect (57), which *suggests new therapies are needed to obtain larger effects.*

Moreover, the only study to examine the effect of therapy on PTB was an RCT conducted in Spain and France to evaluate the Tourne approach versus usual care to reduce depressive symptoms (58). The Tourne approach used humanistic and cognitive techniques during 10 antenatal group sessions for both the woman and her partner. Nurse midwives were facilitators. Depressive symptoms were not significantly reduced; however, there were major differences in the infant outcomes. In the intervention group there were only 3 PTBs (4.4%) with higher birthweights (p =.01), compared to 13 PTBs in the control group (22.4%) (p = 0.003). *Infant outcomes were much improved in women who received behavioral therapy, suggesting the need for trials evaluating both proximal psychosocial risk factors and infant outcomes, such as we are proposing.*

CBT has primarily been used with women who are Caucasian, married and middle class, and not well tested in Latinas; we found only 3 RCTs using CBT targeting depression in pregnancy that included Latina women (59-61). These studies did not specifically address the unique situations associated with Latinas and their distinctive risk factors. Jesse (59) et al. focused on perinatal depression and used traditional CBT for rural low-income minority women. They could not recruit enough Latinas, so the feasibility of this intervention with Spanish speaking Latinas is

still unknown. Munoz (60) focused on Latinas and limited the sample to women with major depression. The 12-week program used social learning concepts, attachment theory, and reality management. It was ineffective in several areas: a) the women completed only 7 of the 12 sessions on average, and importantly, b) the depression scores were not changed after the intervention. Le (61) recruited Central American Hispanics, who, as new immigrants (4 years or less in America), had a low risk for depression. A study limitation was the lack of consideration for psychosocial risks related to acculturation. In sum, studies applying CBT with Latinas did highlight that behavioral therapy can be integrated into the prenatal setting to serve this population. *Our proposed intervention is based on the third wave (newest) generation of CBTs not tested in any studies reviewed in the USPSTF analysis, thus filling a gap and advancing science by testing the newest CBT methods. The three studies using traditional CBT with Latinas focused exclusively on depression, indicating a need for a broader transdiagnostic intervention for other psychosocial distress.*

Acceptance and Commitment Therapy (ACT) (62), a third-wave Cognitive Behavioral Therapy, has a strong evidence-base for effects on depression and anxiety, with burgeoning support for women in the perinatal period. Although it is a CBT, ACT is an innovative behavioral treatment that represents a significant shift in philosophy and perspective. A primary tenet of ACT involves the notion that *avoidance* or attempts to exert strong control of negative emotions, thoughts, or bodily sensations results in and perpetuates psychopathology (e.g., depression, anxiety) (63-65). ACT methods endorse an acceptance rather than a control-based model to promote more flexible and adaptive behavior consistent with client-identified, personal values. ACT has been applied to a myriad of problem areas (e.g., substance abuse, chronic pain) and has a particularly strong evidence base in depression with moderate evidence for anxiety (66, 67). Most studies with pregnant women tend to focus narrowly on perinatal depression, yet ours and other's work (9, 46, 68, 69) suggest a high prevalence of anxiety and stress as well. *Interventions are sorely needed to address co-occurring mental health needs among perinatal women (e.g., stress, depression, anxiety, coping), and therefore a "transdiagnostic" approach, such as ACT, is ideal (67).*

ACT has benefit over other similar treatments in that it links to a theoretical framework with a corresponding comprehensive set of behavioral change principles. Psychological processes involved in psychopathology and target mechanisms for change are identified. Primary processes include acceptance (as opposed to avoidance), values identification, committed action, mindfulness, and cognitive defusion, only a few of which may be targeted with currently recommended CBTs, including interpersonal therapy (IPT). Psychological flexibility is the overarching process comprising the six primary, individual processes, and has been associated with most forms of psychopathology and related problems (70). Most related to the proposal, Stotts (co-I), Villarreal (co-I), Suchting (co-I), and Northrup (co-I) (71) conducted a longitudinal secondary analysis that found psychological flexibility to be a mediator of early (1-2 weeks postpartum) and later (6 months postpartum) depressive symptoms among new mothers of NICU infants. Depressive symptoms in women low in psychological flexibility persisted or increased by 6 months postpartum relative to women who were more psychologically flexible. Many studies support ACT processes as mechanisms of change and potential targets of treatment. In fact, among ACT studies investigating mediators of treatment, about 50% of the between-group differences in follow-up outcomes can be accounted for by differential levels of psychological flexibility (72). *Due to its emphasis on psychological flexibility, we believe ACT is well suited to reduce stress among Latinas as they adapt to the American culture. Other CBT*

treatments have identified very few mechanisms of change for psychosocial distress in perinatal women. The proposed study will fill this gap.

Problem Solving Therapy (PST) (73) targets stressful external problems experienced by pregnant Latinas and teaches tangible problem-solving skills. PST, a behavioral intervention developed from traditional CBT, has been found effective in treating depression (73-76) and anxiety (77,78) Unlike IPT (79) and significant to the proposed study, PST has been better adapted for use within primary and other health care settings and can be administered by physicians and NPs (80). Further, PST has demonstrated effects on mental health outcomes when delivered either individually or in group settings. PST treatment focuses on helping individuals solve multilevel stressors and concrete problems, many of which, our pilot data has found, impact Latinas. ***We contend that a combined treatment of ACT and PST is a much-needed intervention to reduce maternal psychosocial risks for vulnerable Latinas, thus improving clinical practice.***

9.1 STUDY RATIONALE

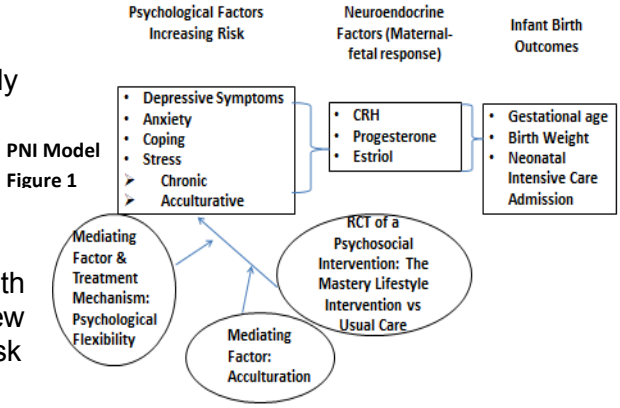
Pregnant Mexican American women (the largest subgroup of Hispanic women), hereafter referred to as Latinas, are at increasing risk for psychological distress which leads to adverse birth outcomes such as preterm birth (PTB, gestational age < 37 weeks) and low birthweight (LBW, <2500 grams) (81,82). The cause of PTB is multifactorial (83, 84), with many of the risk factors difficult to modify (85). Extensive research has been focused on preventing PTB in the United States (US) (86), predominantly testing medical interventions such as drugs (17-alpha hydroxyprogesterone caproate) or cervical cerclage; with minimal focus on decreasing psychosocial risks for Latinas. Women reporting "high" levels of psychological stress are at 25-60% increased risk for PTB compared to those with "low" stress (46). The American College of Obstetrics and Gynecology has endorsed psychosocial screening at least once each trimester in pregnancy (87). Acculturative stress and perceived stress together are known to elevate depressive symptoms in Latinas (88, 89), particularly Latinas who have assimilated into U.S. culture, and are associated with PTB (68, 90-93). Despite this, many care providers do not recognize or diagnose depression during pregnancy; and even if depressed women are identified, few are treated (94). This is a significant unmet need for Latinas (95) leaving them at increased risk of both PTB and postpartum depression (92) which has devastating and long-term effects for mother and child (93). Our prior research, using a psychoneuroimmunology (PNI) framework, has identified psychological risk factors (depressive symptoms, anxiety, stress, acculturative stress, coping) and neuroendocrine risk factors (high Corticotropin Releasing Hormone [CRH], lower progesterone, higher estriol) at 22-24 weeks gestation as strong predictors of PTB in Latina women. The rate of prematurity was unacceptably high in this understudied population of women (as high as ~16% in our previous study) (97). **New interventions targeting additional risk factors need to be identified and rigorously tested** (85).

To address the gaps related to interventions for Latinas, we have developed, and pilot tested the novel Mastery Lifestyle Intervention **(MLI**): a culturally-relevant, manualized psychosocial group intervention that integrates two evidence-based cognitive behavioral therapies **(CBT)** – Acceptance and Commitment Therapy **(ACT)** and Problem-Solving Therapy **(PST**). Our study is unique in that we propose to target psychological risk factors with the MLI and also assess the impact on associated neuroendocrine risk factors for Latinas, based on our evidence (97,98) as well as extensive empirical evidence in other populations (7, -9, 99). This innovative

combination of two interventions during pregnancy is expected to have an effect on clinical outcomes as well. The MLI is a 6-week program designed to be integrated into regular prenatal care to facilitate more comprehensive care delivered by a nurse practitioner **(NP)** or certified nurse midwife **(CNM)**. We have specifically targeted the timing of the MLI prior to maternal biological changes seen at 22-24 weeks gestation in our previous work. *Our pilot study of the MLI demonstrated feasibility, acceptability and a moderate to large pre-post effect size for reducing anxiety, and a moderate effect size in reducing depressive symptoms.* We are now poised to test the MLI in a rigorous RCT conducted in early pregnancy and integrated into a prenatal care setting for Latinas. To our knowledge, this will be the first study to a) explore both the psychosocial and biological effects of ACT and PST and, b) explore the effects of ACT and PST related to improving gestational age, birthweight and NICU admission. We propose the following aims:

Primary Aim 1: Determine the efficacy of the MLI in pregnant Latina women to decrease depressive symptoms, anxiety, perceived and acculturative stress, and to improve coping, with psychological flexibility as a mediating factor and acculturation as a moderator, versus usual care **(UC),** from baseline (14-20 weeks gestation) to end-of-treatment (20-26 weeks gestation) and at a 6-week follow-up (26-32 weeks gestation). **Hypothesis 1:** Participants in the 6-week MLI will have decreased depressive symptoms, anxiety, stress, disengaged coping and increased active coping compared to UC at end-of-treatment and at a 6-week follow-up. **Exploratory Aim 2:** Explore the effect of the MLI, versus UC, on neuroendocrine risk factors of PTB (CRH, progesterone, and estriol) from baseline to end-of treatment. **Hypothesis 2a:** Compared to UC, MLI participants will have significantly lower mean levels of CRH over time from baseline to end-of treatment. **Hypothesis 2b**: Compared to UC, MLI participants will have significantly higher progesterone levels and lower estriol levels (higher progesterone/estriol ratios) over time from baseline to end-of treatment. **Exploratory Aim 3**: Explore the effect of the MLI on infant birth outcomes (gestational age, birthweight, NICU admission). **Hypothesis 3:** As compared to UC, infants from mothers in the MLI group will have longer gestational age, greater birthweight, and less NICU admissions.

Impact: We expect the MLI will provide a greatly needed, novel, feasible, and effective nonpharmacological program added to the toolbox of treatments assisting providers to improve health during pregnancy. This work is consistent with the mission of NICHD to improve prenatal health, particularly in relationship to health disparities. It is an important step in identifying new pregnancy interventions to possibly reduce the risk of PTB.



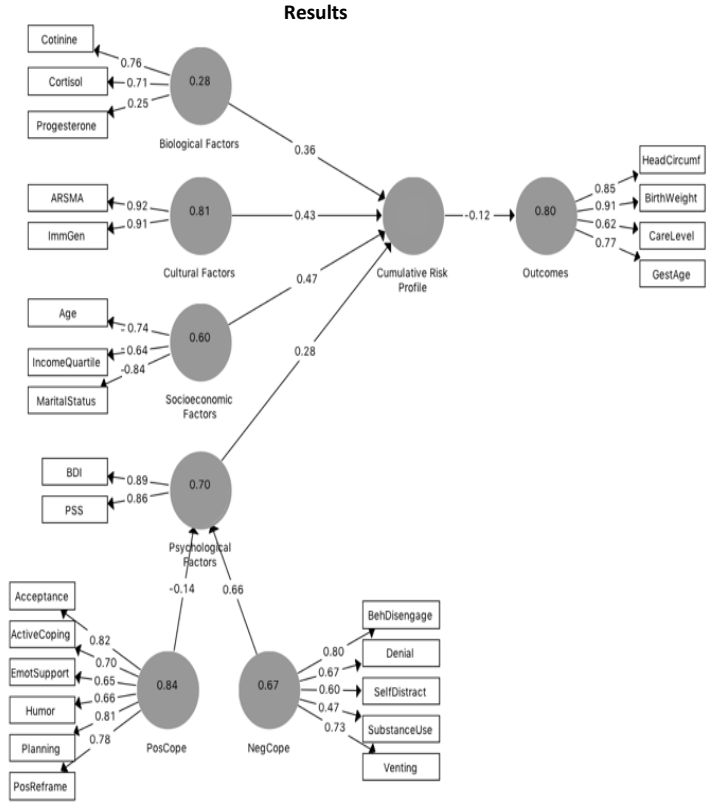
9.2 BACKGROUND

Conceptual Framework. We have based our previous work for the last 20 years on the psychoneuroimmunology (PNI) model. This model (Figure 1) of "psycho," or psychological factors (such as depressive symptoms, anxiety, etc.), with neuroendocrine factors (such as hormones and corticosteroids), with immunological factors (inflammatory markers, infections) predicts health outcomes. From this framework, we have tested depressive symptoms, anxiety,

stress, and coping as psychological factors impacting birth outcomes in Latina pregnant women. Our evidence, as well as extensive evidence from the literature, indicates the importance of testing a model to reduce psychobiological risk and, subsequently, poor infant outcomes (100-104).

Observational Results. In our last study, PI-Ruiz-R01NR07891, we had a sample of 515 pregnant Latinas. We conducted an observational study at 22-24 weeks gestation and measured acculturation, progesterone, cortisol, cotinine, age, marital status, income, stress, depressive symptoms, and coping. These risk factors were tested as predictors of a higher-order latent factor, that we named the *Cumulative Risk Profile* (98). We hypothesized that the cumulative effect of biological, cultural, socioeconomic, and psychological risk factors would predict neonatal health, represented through a latent outcomes construct. We sought to evaluate the strength of the factors that put these women at risk for poor outcomes by a predictive structural equation model. Consistent with our hypotheses, poor birth outcomes were predicted by risk factors at multiple levels of analysis, including biological, cultural, socioeconomic, and psychological. The tested empirical model of a *Cumulative Risk Profile* predicting poor birth outcomes (lower birth weight, decreased gestational age, more NICU admissions) had a good model fit and was scientifically rigorous (See Figure 2). Young, low income, single (socioeconomic factor), and greater acculturation (cultural factor) have the highest regression coefficients predicting the risk of having a poor pregnancy outcome. Stress and depressive symptoms were also important psychological factors predicting risk and are modifiable, unlike most other risk factors. Coping, particularly negative coping as noted from the different subscales in this figure, predicted an increase in depressive symptoms and stress, suggesting another treatment target. *These results not only demonstrate our ability to conduct large studies but also provide the rationale to target modifiable psychological risk factors to prevent PTB. The MLI is a targeted intervention to reduce stress and depressive symptoms and to increase adaptive coping.* We also have results using latent profile analysis to identify characteristics of low-, moderate-, and high-risk groups for PTB (97). The low-risk group (n = 157) had 7.7% PTBs (n = 12). Characteristics of women in the low-risk group: slightly older (mean = 25), married (56%), the least acculturated (more Spanish speakers, fewer years in the U.S., more identification with Mexican cultural identity) as compared to the other two groups.

Figure 2 Cumulative Risk Profile SEM Results

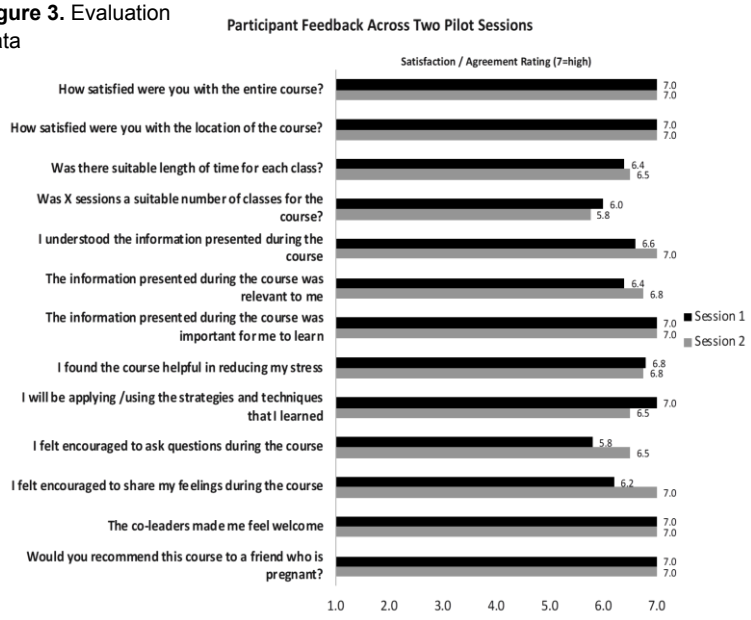


group for PTB (*n* = 272) had 12% (*n* = 32) PTBs. Characteristics of the moderate-risk group: average childbearing age (mean = 24), slightly fewer married women than the low-risk group (48%), more acculturated (greater English speakers, more years in the U.S., mean between second and third generation) as compared to the low-risk group. Depression scores were low (mean = 9 on the BDI), and coping was more active vs. avoidant. The high-risk group (*n* = 86) had 16% PTBs (*n* = 13). They were younger women (mean = 23), significantly fewer married, (26% married; *n* = 21), the most acculturated (more English proficiency, the least Spanish proficiency, and the longest time in the U.S.) as compared to the moderate- or low-risk group. They had high scores on the BDI (mean of 22 or moderate depression). They also had the highest scores on disengaged coping and lowest scores on active coping. *These results indicate an association between psychological symptoms and PTB and the need to target psychological factors, particularly disengaged, avoidant coping, with pregnant Latinas.*

Development of the Mastery Lifestyle Intervention (the MLI): Rationale and Justification. The MLI is a manualized psychosocial group treatment that integrates two evidence-based interventions – Acceptance and Commitment Therapy (ACT) and Problem-Solving Therapy (PST). ACT is a contextual behavioral treatment systematically applied and investigated in diverse settings, with diverse populations and cultural backgrounds, and for a variety of behavioral health problems (62,105,106-108). ACT can easily be done in group formats and has reduced depression in various populations. For example, in a recent study (108), stroke survivors who received group-based ACT for 4 weekly 2-hour didactic sessions, as compared to a treatment-as-usual group, had significantly reduced depression and increased hopefulness with medium effect sizes. ACT helps increase psychological flexibility, identify personal values, and implement behavioral changes that are personally meaningful to the individual (i.e., committed action). Kashdan and Rotterburg (109) define psychological flexibility as "*the measure of how a person: (1) adapts to fluctuating situational demands, (2) reconfigures mental resources, (3) shifts perspective, and (4)* ***balances competing desires, needs, and life domains."*** This concept addresses much of what Latina women are required to do in pregnancy and as they acculturate. PST is a behavioral treatment that teaches recognition of how one orients to a problem and focuses on the development of specific problem-solving skills. It is flexible in its application and works well as part of a larger, integrated treatment package for different populations. PST provides training about how to better resolve and cope with stressful life problems (75) has been used as a stand-alone treatment, and has been effective in pregnancy (110, 111).

We have integrated ACT and PST in the MLI to complement and build on each other. ACT

Figure 3. Evaluation Data



enhances flexibility in responses to internal stimuli (thoughts, feelings, physical sensations), while PST teaches more concrete problem-solving skills in the external environment. Both assist women in pursuing valued goals. PST is a natural extension of the ACT process of committed action. ACT and PST both teach effective coping strategies related to changes and roles Latinas may face due to pregnancy as well as acculturation. Dr. Stotts' and Villarreal have integrated ACT with other behavioral interventions in their study with perinatal women who use illicit substances [NIDA R34 DA041465]. The MLI facilitator manual and the participant handbook have been translated into Spanish and are in the process of being back translated into English currently.

D.2.c. Pilot Study Results of the Mastery Lifestyle Intervention (MLI) (112)

Feasibility. We conducted a one arm, pre-post test pilot study that included 3 cohorts with 15 participants, each using the inclusion/exclusion criteria in the proposed study. All but one of 15 participants attended 100% of the sessions. Several attempts at recruitment were initiated (e.g., recruitment with a research assistant not part of the obstetrics practice), however most efficacious was contracting a medical assistant from the obstetrics practice to recruit pregnant women at the care site and holding the sessions in the lobby of their provider, resulting in better recruitment and attendance rate for the sessions. The pilot trial elucidated that the recruitment window needed to be 14-20 weeks gestation to maximize the number of participants. Six sessions were well tolerated and attended, and we will continue that number for the proposed RCT. The use of electronic tablets was highly feasible; the use of the tablets by participants worked well.

Acceptability. Figure 3 above provides evaluation data from the MLI pilot participants. Women ranked the answers on a survey on a scale of 1-7, with 7 being excellent and 1 being very poor. Participants reported that 6 sessions from 1.5 to 2 hours appeared to be ideal. Based on these results, we have added more group engagement.

Pretest and Posttest Results. From pre- to post-assessment, the intervention reduced anxiety and depression and negative coping (effect sizes ranged from -.30 to -1.5 for anxiety and -0.45 to -0.58 for depression). Positive coping (e.g., use of emotional or instrumental support, use of humor; acceptance) was increased as well, with subscale effect sizes ranging from 0.2 to 0.39. Negative coping (e.g., avoidance and distraction) was decreased with subscale effect sizes ranging from -0.28 to -0.61. **Our pilot results were positive and support proceeding to a larger RCT to further establish efficacy for the MLI**.

9.3 RISK/BENEFIT ASSESSMENT

9.3.1 KNOWN POTENTIAL RISKS

What are the risks of taking part in this study?

For <u>the MLI (or intervention) group</u>:

- There is a risk that the MLI may not be as good as traditional therapy for anxiety, depression or stress.
- There is also a risk that a participant can have some emotional discomfort from taking part in the MLI group. Due to the nature of the MLI group sessions, there may be sensitive emotions or problems revealed. To decrease this risk, if needed, the study team will have a list of resources we can give to the

participants should they experience discomfort.
- At the first group session, we will discuss the rules of the group session in order to minimize the risk of participation and maintain your confidentiality. **

**Exceptions to the confidentiality rule include: 1) if child or elder abuse is revealed, the session leaders are required by law to report that to child or adult protective services; and 2) if a participant indicates suicidal or homicidal thoughts (group leaders may disclose this information to protect the participants or others [in accordance with Texas law]).

Discomforts **for either group** associated with this research include:
- There is a minimal risk of mild pain or discomfort, bruising and swelling from the blood draw at the puncture site, or there may be dizziness or fainting. There is a small risk of infection. We will apply pressure with a sterile gauze dressing for several minutes to avoid bruising and infection and assist anyone with smelling salts if they are faint.
- A participant may get tired or bored when they are filling out the questionnaires. The study team will make sure the participant does not have answer any question they do not want to answer.
- A participant may have mild emotional discomfort from answering the surveys.
- With research participation, there is a small risk of a loss of confidentiality. Research personnel will work hard to maintain participant confidentiality (privacy). We will do our best to maintain participant privacy throughout your time in the study.

9.3.2 KNOWN POTENTIAL BENEFITS

What are the potential benefits to taking part in this study?
- The MLI group will be facilitated by a nurse practitioner, a licensed advanced practice nurse, who will be able to address anxieties or problems related to pregnancy and mental health
- Improved coping
- Decreased stress
- Decreased depression and anxiety symptoms
- Improved relationships with the partner of the participant
- Improved sleep
- Benefit to other pregnant women in the future
- Lowered risk for preterm births as a result of improved emotional health in the MLI group

9.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Protections against Risk: There should be minimal risks from participating in the research study. The risks to the participants related to the effects of untreated depression and anxiety on the fetus are much greater than any of the risks delineated in participating in the study. A physical risk is that of bruising and /or pain from the venipuncture site. Pressure will be applied with a sterile gauze dressing for several minutes to avoid bruising. Women may have some emotional distress from answering the questionnaires. There is some risk for the participants to travel to the sites either by bus or by car, but this risk is no greater than they have for everyday activities that they travel to or risk to come to their prenatal appointment. In addition, the fact the sessions are facilitated by a certified NP gives an added benefit as she should be able to handle medical concerns that may arise. The group sessions will be conducted either on-site in the office of Dr. Chavez, or via phone or electronic tablets. The group sessions will be scheduled for when there are no other office visits to ensure privacy if conducted in person.

To minimize any potential risks, we will use the following protocols:

Handling of Depression or Suicidality: Depression questionnaires will be completed at 14-20 weeks gestation, at 20-26 weeks gestation, and at 32-36 weeks gestation for participants in either group. The CRA will review the baseline score for the CES-D immediately on-site after the participant completes it. We will consider:

- The CRA or CRC will advise Dr Chavez if the score on the CES-D is > 30 so that he may make an immediate referral for treatment of severe depression.
- The CRA will also complete an "Adverse Score Follow-up Care Report" to indicate the score, action taken, and any additional notes that might become important should reporting to the IRB become necessary. In the MLI group, the NP facilitator will monitor depression and suicidality while conducting the group therapy. In the UC group, providers will monitor women as is customary in their practice and follow the previously established standard of care.

Handling of Disclosure of Domestic Violence: Although not a focus of this study, it is possible that a woman would disclose interpersonal violence during or after a group session. Our initial curriculum packets will contain resources and supports in the Houston community for women experiencing interpersonal violence. If domestic violence is revealed, the CRA or NP will individually and discretely talk to the woman to see if she would like help developing a safety plan and will offer her a list of resources for domestic violence. The NP should have training and experience assessing for domestic violence, but we will also include a refresher training during our team trainings for practitioners so that all team members know the current, active available resources for women experiencing interpersonal violence. We will encourage women to share their experiences with their prenatal care providers, and, if needed – will inform her care provider on her behalf and with her permission as noted on the Adverse Score Report Form.

Emotional Upset during or after completing questionnaires: Some of the items on the questionnaires may cause emotional upset, particularly as items may cause a participant to consider how she is feeling. If she is not feeling well and is more aware of her feelings during or after completing the questionnaire, the NP will discretely take her to a private area to reassure her and support her. The group sessions should also provide an opportunity for others to offer support. The woman will be reminded that she can check in with her prenatal care provider, too. Although the risk for more severe emotional upset is possible, it is very unlikely and will be

noted on our Adverse Score Report Form if it does occur. In our prior R01s using these questionnaires with 1000+ women this situation did not arise.

Biohazard Safety: Handling of Body Fluids and Universal Precautions: Only sterilized, disposable butterfly needles will be used for drawing blood. Participants will be instructed to let the CRA or CRC know of any problems during the blood draw; however, procedures are such that the risks of problems occurring during blood draws are rare. Pressure will be applied at the venipuncture site to avoid bruising. The CRA will monitor the participant for any problems after the blood draw. All persons handling blood or body fluids will employ strict universal precautions to avoid the spread of blood borne pathogens to themselves or others and use personal protective equipment. Blood will be transported in coolers by the CRA that has had training in blood borne pathogens and universal precautions. There should be no legal risks in obtaining urine for cotinine checks since smoking is legal.

Loss of Confidentiality: Due to the nature of group sessions there may be sensitive emotions or problems revealed by the participants. At the first group session, we will review the rules for the sessions. The first rule is that what is said in the group stays in the group so that people are not afraid to share and help each other.

The only exception to this rule is if child abuse is revealed. For child abuse, mandatory reporting will be done to child protective services by the NP (as noted on the informed consent).

Confidentiality of participants will be assiduously protected. No names of individuals will be shared or published at any time. Each participant will be assigned a unique code number. Only the NP, CRC, and the CRA will have access to the master list of participant names and code numbers with contact information. However, the PI and other investigators will make every effort to not examine this list as they need to be blinded as to groups for analysis purposes. The master list will remain under a protected password for the CRA or NP to use for follow-up. The CRC who will be drawing the blood will know the participant names and numbers of the blood samples and urine samples in order to ensure proper labeling of the biological samples and the questionnaires. Study personnel will remain blinded as to results until the study is completed. Staff at the physician office will not have access to any individual's questionnaire results, laboratory specimens, or data analysis results.

10 OBJECTIVES AND ENDPOINTS

. OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To determine the efficacy of the MLI in pregnant Latina women to decrease depressive symptoms, anxiety, perceived and acculturative stress, and to improve coping, with	The primary endpoints are depressive symptoms, anxiety, perceived and acculturative	Primary antecedents are: depressive symptoms, anxiety, perceived and acculturative stress and coping. Psychological flexibility is a mediator and acculturation is a moderator	We propose that the primary endpoints affect the neuroendocrine response of Corticotropin

. OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
psychological flexibility as a mediating factor and acculturation as a moderating factor, versus usual care **(UC),** from baseline (14-20 weeks gestation) to end-of-treatment (20-26 weeks gestation) and at a 6-week follow-up (32-36 weeks gestation). This objective is to demonstrate efficacy.	stress, and coping at the end of a six-week treatment at 20-26 weeks gestation of pregnancy and at 32-36 weeks gestation to see if the MLI group has improved scores as compared to usual care.	for the antecedents.	Releasing Hormone (CRH), progesterone and estriol in the maternal/fetal response.
Secondary			
To explore the effect of the MLI, versus a usual care group, on neuroendocrine risk factors of preterm birth (CRH, progesterone, and estriol) from baseline to end-of treatment.	Neuroendocrine responses (CRH, progesterone, and estriol) previously demonstrated as causally related to the antecedents and to the infant health outcomes.	The neuroendocrine measures are potential causal mechanisms linking the changes in the antecedents to the improved infant health outcomes.	CRH, progesterone and estriol are all part of the maternal fetal responses to stress, anxiety, and depressive symptoms.
Tertiary/Exploratory			
To explore the effect of the MLI on infant birth outcomes (gestational age, birthweight, NICU admission).	These are clinically important events for the infants in the study to show a possible treatment effect.	Health outcomes of the infants after usual care or after treatment with the intervention to further determine efficacy.	

11 STUDY DESIGN

11.1 OVERALL DESIGN

Hypothesis 1a: Participants in the 6-week MLI will have decreased depressive symptoms, anxiety, and stress, disengaged coping, and increased active coping compared to UC at end-of-treatment and after 6 weeks. **Hypothesis 1b:** The effects of MLI versus UC on depression, anxiety, stress, acculturative stress, and coping will be mediated via psychological flexibility and moderated by acculturation. **Hypothesis 2a:** Compared to UC, MLI participants will have significantly lower mean levels of CRH over time from baseline to end-of-treatment. **Hypothesis 2b**: Compared to UC, MLI participants will have significantly higher progesterone levels and lower estriol levels (higher progesterone/estriol ratios) over time from baseline to end-of-treatment. **Hypothesis 3:** As compared to UC, infants from mothers in the MLI group will have longer gestational age, greater birth weight, and fewer NICU admissions.

This is a Phase 2 trial with only one site.

Design of Trial. Based on our data and data from previous studies, we believe a test of the MLI is feasible, warranted, and will result in successful reductions of distressing psychological symptoms with the potential to reduce PTBs. We propose to conduct a parallel-group (MLI versus Usual Care **UC**) RCT to assess the efficacy of the MLI compared to routine prenatal care, with psychological assessments at pre- and post-intervention, as well as 6 weeks after the sessions are complete. Our clinical research associate (CRA) will recruit eligible pregnant Latinas at 14- 20 weeks gestation from the office of Dr. Anthony Chavez, in the Texas Medical Center, who serves a large Hispanic population. We selected this gestational age as it is late enough to avoid miscarriages and early enough to possibly prevent biological responses associated with PTB**.** MLI group sessions will be conducted in the providers' office weekly for 6 weeks and last 1 1/2 hours. Alternatively, we will meet via telehealth over an electronic platform that is encrypted for safety of the group, either over telephones or electronic tablets. The MLI will be delivered in either English or Spanish. We will minimize the potential for contamination between groups as participants in the UC will be scheduled only when there are no group sessions for the MLI.

Random Assignment. The random assignment of groups will be completed by our statistician, Dr. Suchting, using a SAS, version 9.4 (Cary, NC), fixed random number generator. He will seal the assignment of all groups in opaque envelopes, numbered 1 to 29, to be opened by the CRA on the day after 6-8 women have consented. Two methods of random assignment were considered: 1) randomly assigning *individuals* to either the MLI or UC, or 2) randomly assigning formed *groups* to either the MLI or UC. We chose randomization by group, which will be conducted sequentially to decrease potential contamination across treatments as only one treatment will be conducted at a time, facilitating follow-up through the post-treatment period. We are aware that in forming groups, some participants may experience a short waiting period prior to beginning group treatment to allow for adequate numbers in each group. All groups will be randomly assigned to one of the two treatment conditions. Group conditions will not be revealed to staff until after collecting baseline data collection. Once 6-8 patients have been recruited, consented, administered the intake/baseline assessment, and had their blood drawn, they will be notified by the CRA and scheduled for either MLI or UC. Our first group will begin in September of 2021, and we will adjust session formats to electronic delivery as needed, based on the current status of the COVID-19 epidemic. Envelopes will be locked at UTHealth, only Drs. Suchting and Northrup (Co-Investigators) will have access.

Number of study groups and duration of intervention. Considering we may have both

refusals and exclusions; we anticipate a conservative estimate of 6- 8 women recruited every 6 weeks. In the first year, we will start recruitment the fourth month after funding, first group after 6-8 women are recruited and randomized to the intervention or UC. We will be able to recruit 18-24 women (3 groups). We propose 6-8 women/group with 8 groups/12 months for years 2-4. Year 5, we will only need 24 more women (3-4 groups). The total of the MLI and UC groups together will be 234 women over ~4 ½ years. This will allow for a ~15% attrition rate. We estimate we will screen 351 women to reach our enrollment target of 234. The data collection for the infant outcomes will be 4-8 weeks after the 32–36-week last data collection for the participants.

The Intervention. Table 2 gives module content, processes, and goals for the MLI.

Table 2. MLI Content, Processes & Goals

#	Session Content	ACT/PST Processes	Goal of Topics
1	A. Impact of stress on physical and emotional wellbeing B. Strategies to deal with stress: Externalize, Visualize, Simplify, Acceptance C. Introduce values - Identify values in various life domains	Identify and manage stress Identify values	Defuse from stress to avoid biological responses Identification of valued life areas
2	A. Identify and describe barriers that impact problem-solving skills: negative feelings, negative thinking, feelings of hopelessness B. Defusion exercises: learn to look AT thoughts rather than FROM them. C. Introduce and practice two problem solving skills to live according to identified values D. Introduce "Stop, slow down, think and act" and rational problem solving	Identify barriers to solving problems Defusion	Understand barriers to achieving values Problem solving ways to get around the barriers
3	A. Introduce & practice generating alternative solutions to overcome barriers to reach value-related goals B. Strategies: a. Quality principle; b. Deferment principle; c. Getting unstuck	Committing to Action	Identification of obstacles to problem solving Define alternatives to solve problems
4	A. Predict Consequences of Alternatives; B. Generate Pros and Cons	Evaluation of solutions Psychological flexibility Acceptance	Determine the best solution; Possible reevaluation if no best solution
5	Develop an Action Plan, carry plan out; Monitor, evaluate, reward self	Commitment	Development of an action plan
6	Summary of content and skills & how to apply in one's life Note: Mindfulness exercises are at the end of each session		Review of content and plan to apply in everyday life

The techniques from ACT facilitate experiencing difficult thoughts and feelings rather than avoiding them. Paired with mindfulness, cognitive defusion allows women to acknowledge their troubling thoughts/feelings and view them from a distance rather than believing them as literally true (e.g., "I can't handle having another baby.") The goal is to change the *impact* of distressing thoughts and feelings rather than trying to eliminate the thoughts and feelings themselves, which may alter biological responses in the body. Indeed, mindfulness alone has been associated with reduced distress (109) and changes in the brain (110). PST techniques include making effective decisions, generating creative solutions, and identifying barriers to reach one's goals. We made cultural modifications (e.g., considerations for family roles and hierarchies, culturally relevant metaphors, mindfulness

exercises) to the MLI to make it more beneficial for pregnant Latinas. We will hold six weekly sessions starting at 14-20 weeks gestation to 20-26 weeks gestation lasting ~1 ½ hours. This is the average number of sessions delivered in other intervention studies using CBT in pregnancy and was supported in feedback from our pilot sessions. Staff will make every effort to schedule the participant's prenatal visits in the morning prior to their group session in the afternoon to avoid separate trips (transportation will be provided if separate trips are necessary at any point). We will give participants in the MLI group a participant handbook in either English or Spanish that has space for reflection and activities to complete at home. We have refined our facilitator handbooks extensively. Conducting the MLI with groups is feasible, acceptable, and advantageous as it is a) cost-effective, b) allows for group support and building a social network (important to Latinas) (113), and c) encourages good role modeling (113). A recent meta-analysis (114) found no significant differences in effectiveness in individual versus group formats for CBT.

Rationale for the use of NP or CNMs. Authors of systematic reviews (115,116) recommend the use of CNMs/NPs to improve maternal mental health. They argue that there is a great need for innovative ways to provide effective mental health interventions for pregnant women. NPs scope of practice includes the treatment of mental health (117). Interventions such as Creating Opportunities for Personal Empowerment (COPE) (118-121) (a 2nd generation CBT) have successfully used registered nurses as well as NPs as facilitators with good outcomes. NPs were also effective in our pilot studies. *NPs/CNMs are ideal facilitators because of their knowledge of both physical and mental health aspects of pregnancy; a focus on both may reduce prematurity risks.* NPs or CNMs will facilitate the groups with participants.

Control or Usual Care (UC) Group. UC will receive standard, traditional individual prenatal care under the schedule of visits recommended by the American College of Obstetricians and Gynecologists. Via the UC group, we will be able to discern if the MLI reduces psychosocial risks more effectively than does usual information and advice provided as part of current practice. Women needing mental health treatment in UC will be referred to an approved mental health specialist as well as consulting their insurance provider.

11.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The selection of usual care for the comparison group is based on the current baseline for prenatal care, i.e., no intervention for mental health, unless pathology is diagnosed and then treatment is referred. The emotional wellbeing of the participants is not routinely assessed in care, unless it is a simple screen for depression. Inclusion of a usual care group allows for evaluation of treatment outside of prenatal care (i.e., psychologist or psychiatrist), including use of medications. The purpose of the intervention is to ensure emotional wellbeing as part of the patient's prenatal care. As noted, we will avoid MLI group sessions when the usual care group is being seen to avoid contamination from one group to the other.

11.3 JUSTIFICATION FOR INTERVENTION

Please see Section 4 under study design for the justification for data collection related to infant outcomes and length and number and frequency of intervention contacts. The intervention was developed for the Hispanic culture as noted in the description of the intervention. Minimal acceptable participation in the intervention will be 5 of 6 sessions. We will control for number of sessions in our data analysis.

11.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline first assessment, at least 5 intervention sessions for the experimental group, a second assessment, and the third and final 6-week follow-up assessment for both groups.

The end of the study for participation is defined as the completion of the assessments for both UC and MLI groups.

12 STUDY POPULATION

12.1 INCLUSION CRITERIA

Inclusion criteria are: a) providing informed consent; b) ability to read and speak English or Spanish; c) pregnant at 14-20 weeks gestation with one fetus, intrauterine pregnancy, gestational dating will be reviewed before enrollment via ultrasound administered per standard of care; d) self-identification as Latina of Mexican heritage; e) age 18 to 45 years; and f) born in Mexico or U.S. born and currently living in the U.S.; g) Medicaid or other government supported insurance; h) women who score 10 or greater on the CES-D (possibility of mild depression) OR 5 or greater on the Generalized Anxiety Disorder-7 scale (GAD-7) (mild anxiety), OR greater than or = to 14 on the PSS (mild stress); i) willingness to adhere to the MLI regimen or usual care regimen.
Justification for prescreening scores of the participants: The aim of this project is to both prevent and treat problems that Latina pregnant women may have with their emotional health.

12.2 EXCLUSION CRITERIA

All individuals meeting any of the exclusion criteria at baseline will be excluded from study participation as noted below:
Exclusions after initial review of the electronic health record (EHR) are: a); major systemic infections such as HIV, hepatitis; b) <18 years of age; c) enrollment in a prenatal program such as the Nurse Family Partnership; d) severe cognitive or psychiatric impairment per judgment of providers, that precludes cooperation with study protocol; e) inability to read English or Spanish. Women who develop GDM after enrollment in the study will remain in the study. Development of hypertension or preeclampsia, pyelonephritis, or GDM will be considered an effect modifier in analysis of infant outcomes. Current antidepressant use will not be exclusionary. Further rationale for the exclusion criteria is:

- Only singleton pregnancies are included as the mechanisms of PTB are thought to differ with multiples.
- We do not exclude participants based on language (English or Spanish) spoken. We expect heterogeneity in language spoken and expect that there may be women who use both languages. Our prior study findings indicate that the risk of PTB is greatest among

English-speaking and bilingual women, although we believe that all women will receive benefit from the MLI.

- Girls <18 are excluded as the intervention is designed to improve emotional wellbeing and quality of life in mature adults; girls <18 may not be cognitively ready for the adult intervention and may need an intervention tailored to their stage of development. Girls under 18 also have a different set of risks than women over 18 years of age.
- We will control for the use of progesterone treatment statistically.
- Women who develop gestational diabetes after enrolling in the study will remain in the study.

Anyone who develops hypertension, pyelonephritis, or gestational diabetes will be noted in the database and be considered in the category of effect modifier in analysis but will remain in the study.

- At enrollment or during the study, anyone who is prescribed antidepressant or anti-anxiety medications will be eligible for the study. We will make note of it and control for it in analysis.
- We will use the following questions that are typically used to screen for Serious Cognitive or Psychiatric Impairment:
    - Are you currently taking any medication for symptoms related to a mental illness such as schizophrenia, schizoaffective, or bipolar disorders? If so, for what symptoms?
    - Have you ever been diagnosed with a mental disorder or illness such as schizophrenia, schizoaffective, or bipolar disorders? If so, what was the diagnosis?
    - Has a mental health professional such as a social worker, psychologist, or psychiatrist ever told you that you had a diagnosis of schizophrenia, schizoaffective, or bipolar disorders? If so, what was the diagnosis?
    - Has a medical provider such as your primary care doctor or nurse practitioner ever told you that you had a diagnosis of schizophrenia, schizoaffective, or bipolar disorders? If so, what was the diagnosis?

12.3 LIFESTYLE CONSIDERATIONS

N/A

12.4 SCREEN FAILURES

Our prescreening of the prenatal chart and the use of three different instruments to include participants that at least have mild anxiety, depression or stress should be sufficient to avoid the need for screening failures.

12.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Sample and Setting. Dr. Chavez and his associates' practice in the Texas Medical Center in Houston see ~40 new pregnant women monthly, of whom 80% are less than 10 weeks gestation or 32 eligible women monthly, yielding 16 eligible women monthly. In our last study using this practice and inclusion criteria, 61% of patients had scores on the CES-D of 10 or

greater (mild depression), and 30% had scores of 16 or greater (moderate to severe depression). We will use the CES-D to prescreen for scores of 10 or greater (mild depression), or the GAD-7 with a score of 5 (mild anxiety) or greater and the perceived stress scale PSS with 13 or greater. Considering we may have both refusals and exclusions; we anticipate a conservative estimate of 6-8 women recruited every 6 weeks. In the first year, we will start recruitment in the fourth month after the study has been funded and will be able to recruit 18-24 women (3 groups of 6-8 women each). We propose 6-8 women/group with 8 groups/12 months for years 2-4. Year 5, we will need 24 more women. The total of the MLI and UC groups together will be 234 women over ~4 ½ years. This will allow for a ~15% attrition rate. We estimate we will screen 351 women to reach our enrollment target of 234. In the same obstetrical practice from the last study, 66% spoke English, 24% were bilingual, and 10% spoke Spanish only. The women in our last study from this practice participated at a high rate; 80-85% of those approached consented. They identified with Ms. Pecina, the recruiter (CRA) (whom we will use again) and trusted the endorsement by Dr. Chavez. Dr. Chavez reports that about 20-25% of his Latinas are not documented; therefore, we can recruit both documented and undocumented participants. We plan to offer the MLI in separate sessions for English and bilingual English/Spanish versus Spanish speakers only.

Procedures for Recruitment, Consent, and Data Collection. Our clinical research associate (CRA) will coordinate with the staff of Dr. Chavez to identify Latina pregnant women prior to 14-20 weeks at their first prenatal visit. This will be done by the staff looking at due dates of the patients and if they have Spanish last names. We will place flyers and posters as informational materials in the office and the restrooms. The CRA will be housed at the practice site making the feasibility of ongoing screening easier. The CRA will give the provider a list of potential participants each day possible participants are to be seen for their prenatal visit, and the provider will introduce the study. He will recommend that the participant discuss the study with the CRA after their prenatal visit if they are interested. If the participant is interested in the study, the CRA will review at this visit (Visit 1) the exclusion/inclusion criteria for the participant and review the scores for the CES-D, GAD-7, and PSS. The CRA will plan to obtain informed consent, if possible, then. At a second visit (visit 2) (if the participant cannot stay for data collection after informed consent) baseline assessments will be administered, and biological samples will be collected. To ensure blindness of the data, the CRA will transfer the electronic data directly to Dr. Thomas Northrup, Co-I over REDCAP that is Internet based. Randomization to UC or MLI groups will occur by Dr. Suchting (data analyst) after 6-8 participants have consented. The CRA will call the participants and let them know as soon as possible after randomization as to which group the participant is in.

Post-treatment data collection will occur immediately after the last MLI session or 20-26 weeks for the UC group, and again at six weeks follow-up for the final in person visit. Every effort will be made to coordinate data collection visits with prenatal visits. If the participant does not come for a second data collection visit, the CRA will make a home visit to obtain the data. The CRA is also a community health worker and has had lots of experience with home visits with Latinas. **Rationale for the six-week follow-up data collection after treatment:** We believe it is important to assess potential ongoing effects of the MLI to decrease psychological risks in the third trimester prior to delivery. The NP not facilitating the MLI (thus she will be blinded) will collect prenatal data for both groups as well as infant outcomes.

Processes for Each Group.

The private practice office will serve as a place to host group sessions. One group will

run at a time, either the MLI or UC. Groups will run every week for 6 weeks with MLI sessions lasting about 90 minutes. The last session (Session 6) will require an additional 1.25 hours of time to accommodate completion of study questionnaires and biologic data collection (blood, urine). For the UC, the second data collection will require about 1.25 hours for data collection. The final data collection for both groups will require less time as there will be no biological measures collected, so about an hour of time.

The providers' office has comfortable chairs and available paid parking. Sessions will start at 14-20 weeks gestation and continue through 20-26 weeks gestation. A 14-20-week window will avoid women who may miscarry yet will be early enough in the 2nd trimester to enhance the probability of expected outcomes. Each session will be led by a NP facilitator with the same NP conducting all sessions for each group. In order to keep the NP blinded as to outcomes, the NP not facilitating the sessions will data collect from the prenatal chart and from the hospital delivery record.

Ms. Pecina, the CRA, and the CRC, Ms. Estrada, will data collect before Session 1 and after session 6, performing venipuncture, testing urine specimens, and transporting samples to Microgen laboratory for storage. The same process for biologic samples and questionnaire data collection will be followed for both groups. As much as possible, we will hold all sessions at the same time of day throughout the study to control for diurnal variability. Ms. Pecina will be trained by the PI in the collection and safe storage/transport of biological samples. All specimens will be transported to Microgen laboratories within 24 hours of collection either by the CRA or the CRC. To avoid biased results, Ms. Pecina will administer questionnaires using an electronic tablet device but will not participate directly with the groups. The questionnaires will be completed in a private room(s) in the office to avoid the effect of social expectations on responses. We will clarify questions only, not discuss answers. To avoid bias, the NP that is not the group facilitator will collect data from the prenatal chart. For infant health data, the NP will enter delivery data from the delivery records directly into an Excel database on the encrypted shared drive at UT Health.

Retention and Missed Sessions. We will follow a protocol that resulted in 87% retention in prior studies (122): 1) when obtaining informed consent, the CRA will read with the women a "*Compromiso*" (Commitment) pledge to complete all 6 sessions (122); 2) we will collect alternative contact information for each participant and conduct multiple reminder phone calls if needed (123); 3) the NP will report group attendance to the CRC who will track attendance across the duration of the study with Dr. Northrup and create a weekly and summative attendance/attrition report; 4) the PI will review attendance and attrition rates weekly; 5) the NP will phone or text any participant who misses a session to encourage continuation and assist with issues related to attending the sessions; 6) incentives will be provided for the completion of data collection instruments at baseline, during treatment, and follow-up; and also 7) maintain positive working relationships with family members. Dr. Stotts and her team have extensive experience and strategies, retaining participants in treatment and follow-up. In similar samples, Dr. Stotts and team have achieved >85% retention rates. To evaluate participants' satisfaction with the content and delivery of each session, Likert-type measures will be used at the end of each session. We will use these evaluations to examine factors that may affect attrition, such as timing, place, and day of the week, as well as overall satisfaction with the program. The CRC will coordinate with the NP to call participants that miss a session. The NP will review with them individually the content of the session over the phone using the content of the facilitator's manual. Although the call will not have the benefit of the effect of the group, it will at least allow

the participant to keep up with the knowledge from the module. We will use data about missed sessions to assess dose response.

Although we have had a successful experience recruiting out of Dr Chavez's private practice, if our recruitment lags or we are not able to retain the participants as hoped, we will then seek using one of the obstetrical and gynecological clinics at UT Health or private physicians close to Dr Chavez's practice. This will allow a backup plan should we not meet milestones at the end of year 1.

In addition, we may use the "Fireside Chat" that has been used previously by Dr Northrup and Dr Stotts, as another way to increase retention (124). The Fireside Chat has been used in all of Dr Stotts studies (prior to randomization) with all participants to give them an overview of study participation and help them proactively think through difficulties related to meeting study requirements (e.g., managing other responsibilities, such as work, school, or caring for other children (124). Topics covered in the baseline (pre-randomization) Fireside Chat are often revisited with randomized participants who may be having difficulty with participation later in the study. A study-specific Fireside Chat will be adapted from previous studies done by Dr Stott and Northrup (usually delivered between consent and randomization) to allow participants to feel more comfortable with the study team and procedures. This is also an extra opportunity to ask additional questions about participation, while staff provides non-judgmental information and answers.

Dr. Northrup will also generate weekly reports for team meetings and coordinate with the CRC that will show study flow from pre-screening the electronic health record all the way through the final study visit. This study flow diagram is created by a SAS syntax file outputting study data to Excel, which is then imported to Microsoft Visio to produce a highly detailed CONSORT style diagram. Once the SAS syntax is written (one-time event) by Dr. Northrup, the Visio Consort can be refreshed by any team member by rerunning the SAS file and refreshing the data in Visio (in a matter of minutes), providing real-time reporting of study trends across all areas of study. The team uses these reports to scrutinize trends in screening, consenting, refusal reasons, recruitment, and follow-up completion. Further, detailed individual-participant information is also part of these weekly reports so that participants with adherence issues are identified quickly during weekly rounds on every participant in the study. Similarly, project staff may run these reports in real-time as often as needed.

Once challenging participants are identified, the research team will engage in considerable brainstorming/problem-solving to ensure the completion of the intervention and any follow-up visits in a large diverse city such as Houston. In Dr Stotts and Northrup's previous study, intervention and follow-up retention rates exceeded protocol expectations. We plan to have a designated cellphone for participants to text or call to reschedule/schedule/confirm upcoming visits. The project cellphone will be covered by the CRC 24 hours a day. Facebook, Instagram and Snapchat have also been employed by Dr Stotts and Northrup to connect with participants. Project staff sends messages or make calls in each participant's preferred medium (i.e., e-mail, social media, text, or voice call). At baseline, via the IRB-approved consent form, we will obtain permission to contact participants via multiple methods (e.g., text and social media). These communication methods will be begun immediately, within hours, of a missed visit.

If the CRA or CRC is not successful with engaging/reengaging a participant, then a senior member of the team, such as Dr Ruiz or Dr. Stotts, will reach out to participants to problem-solve missed visits. Further, we will mail missed-visit letters, contact other family members or friends (i.e., "locators" identified during the consent process), and the CRA will drive by participants' homes to engage a participant or leave a "hang tag" on the door if no one

is home. To increase adherence, appropriate incentives (e.g., monetary) commensurate with participants' time and effort are planned for distribution. Research staff will make every effort to let participants know they are valued and appreciated. Staff will use non-judgmental language and try to help participants enjoy their time in the study as other methods to improve retention. Feedback from the pilot study has been incredibly positive related to acceptability and retention.

Participant Incentives. The CRC will ensure that each participant receives money after data collection visits, even if a participant does not complete the entire study, regardless of which group they are in. The participants will receive: $40 after completing first data collection (14-20 weeks of pregnancy), $20 at midpoint after completing the 2 additional questionnaires, $60 at the third data collection visit, and $60 at the fourth and final data collection visit (32-36 weeks of pregnancy). If a participant misses a time of data collection, the CRA will contact them and potentially make a home visit if there is no way they can come to the office. The CRA will provide the appropriate money after data collections are complete. Therefore, for either usual care or MLI group, a participant may potentially receive a total $180 for participating. The participants may also be eligible for parking reimbursement for MLI group sessions held in Dr Chavez's office.

13 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

13.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

13.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

***Please see Table 2 under Study Design for session content and goals of the intervention* for the MLI.**

13.1.2 ADMINISTRATION AND/OR DOSING

We will hold six weekly group sessions starting at 14-20 weeks gestation to 20-26 weeks gestation lasting ~1 ½ hours at Dr Anthony Chavez's private office waiting room. Our primary plan is that the participants will interact with each other face to face and the NP interventionist in the MLI group. We may have to use Zoom or another electronic delivery method if the COVID-19 epidemic is still a major problem. We consider 5 sessions to be the minimum for a full dose intervention. Six is the average number of sessions delivered in other intervention studies using CBT in pregnancy and was supported in feedback from our pilot sessions. Staff will make every effort to schedule the participant's prenatal visits in the morning prior to their group session in the afternoon to avoid separate trips (transportation will be provided if separate trips are necessary at any point). We will give participants in the MLI group a participant handbook in either English or Spanish that has space for reflection and activities to complete at home. We have refined our facilitator handbooks extensively. Conducting the MLI with groups is feasible, acceptable, and advantageous as it is a) cost-effective, b) allows for group support and building a social network (important to Latinas) (113), and c) encourages good role modeling (114). A recent meta-analysis (114) found no significant differences in effectiveness in individual versus group formats for CBT.

13.2 FIDELITY

13.2.1 INTERVENTIONIST TRAINING AND TRACKING

Training and Intervention Fidelity. The NP training for the MLI will be facilitated by co-Is Villarreal and Stotts and PI Ruiz. The sequential training elements are the following: a) The NP will complete knowledge assessments pre-independent study and post-in-person training. b) 5-hours of independent study, including reading the MLI manual and relevant empirical literature, plus listening to audio recordings about different components of ACT or PST, c) 8 meetings for 2-3 hours of didactic and experiential training on how to facilitate an MLI including ACT and PST strategies. A brief didactic review of the MLI model, a description of important teaching strategies, and an explanation of logistical considerations for an MLI group will encompass part of the training. The significant and lengthy portion of the training will focus on the practice facilitation of MLI group sessions through role-plays, plus troubleshooting common problems that occur during groups with challenging group members, and d) 2 weeks of practice sessions and 6-weeks of consultation in which the group facilitator implements the MLI for the first time, conducts group sessions, and does audio/video recordings of their group sessions. Co-I Villarreal will review the videotaped sessions and give immediate feedback.

The PI will conduct education and training sessions for the CRA and personnel at the clinical practice site about the study, eligibility, data collection, questionnaire administration, protocol for venipuncture and blood specimen management, and testing and storage of urine samples. Universal precautions will be taught for safe sample handling. The PI will train the NP not facilitating the MLI to collect data from the prenatal chart and hospital record and will evaluate the effectiveness and accuracy of data collection while ensuring blinding.

Co-Is Drs. Stotts and Villarreal will monitor and evaluate the fidelity of content delivery for MLI groups, conducted in the office of Dr. Chavez or via telehealth. Co-I Villarreal will attend or watch electronically the entire first round of group sessions to review fidelity to the intervention. She will give feedback to the NP after the session. After the first set of sessions, Co-I Villarreal or Stotts will evaluate compliance and competence with the protocol via audio/video recording; remedial training will be provided as needed. Thus, the audiovisual recordings are important for quality control and are mandatory for the participants. Compliance with the protocol will be monitored using the MLI Fidelity Checklist (adherence scale). Treatment adherence will be checked by independent raters (who themselves are skilled in the performance of the treatment, e.g., post-doctoral fellows or junior faculty members working with Drs. Stotts or Villarreal) rating randomly selected videos using the adherence rating scale. The scale lists the core elements prescribed in the manual. The rater will indicate on a scale from 1 (none) to 5 (very much) the extent to which the treatment element was present in the recorded session.

13.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Random Assignment. The random assignment of groups will be completed by our statistician, Dr. Suchting, using SAS, version 9.4 (Cary, NC), fixed random number generator. He will seal the assignment of all groups in opaque envelopes, numbered 1 to 29, to be opened by the CRA on the day after 6-8 women have completed data collection for all baseline assessments. Two

methods of random assignment were considered: 1) randomly assigning *individuals* to either the MLI or UC, or 2) randomly assigning formed *groups* to either the MLI or UC. We chose randomization by group, which will be conducted sequentially to decrease potential contamination across treatments as only one treatment will be conducted at a time, facilitating follow-up through the post-treatment period. We are aware that in forming groups, some participants may experience a short waiting period prior to beginning group treatment to allow for adequate numbers in each group. All groups will be randomly assigned to one of the two treatment conditions. Group conditions will not be revealed to staff until after collecting baseline data collection. Once 6-8 patients have been recruited, consented, administered the intake/baseline assessment, and had their blood drawn, they will be notified by the CRA and scheduled for either MLI or UC. Our first group will begin after 3 months of training and start up in 2021 and we will adjust session formats to electronic delivery as needed, based on the current status of the COVID-19 epidemic. Envelopes will be locked at UTHealth, only Drs. Suchting and Northrup will have access. In this manner the research team that will be unblinded will be the CRA, the CRC, the NP or CNM as they will be directly involved with the intervention, data collection and follow up for those participants who miss sessions. These personnel will be trained and strictly instructed not to share ID numbers with the PI or Co-Is unless the reason is approved by the PI. Drs Suchting (data analyst) will not know what participant numbers are with each group and will not be exposed to the individual participants in any way, and the envelopes will be disposed of at the end of the study. Laboratory samples will be labeled with participant ID numbers and will also remain blinded to Dr Stowe and the laboratory technician. The PI, Dr Ruiz, will make every effort to remain blinded as to who is in which group related to the data and participant numbers. Dr Villarreal or Dr Stotts will review the videotapes of the intervention, so they will also be unblinded as to who is in the intervention group but should not know which participant is assigned to which number related to data.

13.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The CRC and the CRA will initiate and maintain an Excel spreadsheet of all participants in the MLI group as well as the UC group. After each group session, the CRC will check with the NP as to who the participants were and log them on the participation log. Mandatory is completion of the two times the questionnaires are to be given and the laboratory assessments for two different times. An active participant will need to have completed 5 of 6 MLI sessions if in the experimental group, both sets of questionnaires for two different data collections, and two sets of laboratory assessments.

13.5 CONCOMITANT THERAPY

N/A

13.5.1 RESCUE THERAPY

N/A

14 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

14.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from the MLI group but not from the study, the participants will complete the remaining study procedures (i.e., completion of second round of questionnaires and laboratory assessment).
If a deleterious clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the PI Dr Ruiz or qualified designee (Dr Stotts) will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected by the CRC at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

14.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, i.e., less than 5 sessions attended in the MLI group or unwillingness to complete questionnaires and laboratory assessments.
- Lost-to-follow up; unable to contact subject (see **Section 14.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study (for example severe depression requiring hospitalization)
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

14.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to receive 5 sessions of the MLI, and study staff is unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails in participating in a required study visit:

- The NP will attempt to contact the participant, reschedule the missed visit within the next week to be conducted over an electronic delivery, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the CRC or CRA will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up]

Please see also Retention and Missed Visits 5.5

15 STUDY ASSESSMENTS AND PROCEDURES

15.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

See also 5.5 Procedures for Recruitment, Consent and Data Collection

Table 3. Self-Report Questionnaires for Data Analysis

Measure	**Purpose; Variable type**	**Times Measured** Baseline =16-20 wks. Time 2 = 20-26 wks. Time 3 = 26-32 wks.	**# Items**	**α**	**Spanish**
MASII Multidimensional Acculturation Scale (127)	Cultural identity; Language proficiency: **Moderator**	Baseline	22	.78-.93	**Yes**
CESD (129)	Depressive symptoms **Primary outcome**	Prescreen, Baseline; Midtreatment (19-23 weeks) for MLI group only. Time 2 and 3	20	.85-.94	**Yes**
GAD-7 (130)	Anxiety; **Primary outcome**	Prescreen, Baseline, Time 2 and 3	7	.89	**Yes**
PSS Perceived Stress Scale (34)	Global measure of stress **Primary outcome**	Prescreen, Baseline, Time 2 and 3	10	.79	**Yes**

MASI Multidimensional Acculturative Stress Inventory (33)	Measure of acculturative stress **Primary outcome**	Baseline, Time 2 and 3	36	.93	**Yes**
The Brief Cope (131)	Positive versus negative coping; **Primary outcome**	Baseline, Time 2 and 3	28	.86-.89	**Yes**
Multidimensional Psychological Flexibility Inventory (MPFI) 132)	Psychological Flexibility **Mediator**	Baseline, Mid-treatment (19-23 weeks), Time 2 and 3	22	.97	**Yes**
Group Climate Questionnaire (133)	Measures if the group is engaged, conflictual, or avoiding interaction; **Covariate**	Time 2 taken by NP and participants	12	.9	N/A

***D.10. Study variables*.** **Demographic variables** include age, marital status, education, insurance provider or self-pay, gravida, para, number of abortions, country of birth, years living in the US, primary language, residence in public housing, and number of times the participant has moved within the last year. Data on income, housing, mobility, and type of insurance will be used to assess socioeconomic status. This data will be collected by the CRA after training by the PI.

We will not ask the participants if they have a social security number, to satisfy the concerns of the scientific review related to Human Subjects. **Obstetric variables**. The NP who has been professionally trained in obtaining obstetrical histories, will collect obstetrical history, last menstrual period and ultrasound determination of expected date of confinement, height/weight for BMI, infections (vaginal or systemic), medications (particularly SSRI use or progesterone) and other prescription or illegal drug use, and any other medical risk factors for PTB (GDM, preeclampsia, history of PTB, etc.) from the prenatal chart. This data will be obtained only after a HIPPA consent has been signed seeking permission of review of the entire prenatal chart. The HIPPA consent will be obtained with informed consent as it is completed at the initiation of the participation in the study. **Psychological and acculturation measures,** listed in Table 3, will be scored as recommended by scales' authors. The team has used these questionnaires extensively. These measures have been tested in Spanish without problems or reliability issues. We will also ask women if they have been receiving any mental health therapy; this is unlikely in Houston, given the limited resources for low-income persons. The NP facilitator will assess group climate herself and for the participants using the Group Climate Questionnaire (134) at time 2 when the sessions are completed, which will be used as a covariate. **Hormones, cotinine**. We will collect all biological samples at Time 1 (14-20 weeks) and Time 2 (20-26 weeks). After drawing the blood, we will centrifuge the blood and separate into aliquots of plasma as done in our previous studies. The blood will be taken to Microgen laboratories by the CRA and will be stored there at -80°C. Progesterone and estriol will be run in batches with ELISAs at Microgen laboratories. We will prepare plasma samples for CRH with Aprotinin 500 IU/ml added and test CRH by radioimmunoassay (RIA; Phoenix Pharmaceutical Incorporated, Belmont, CA) following the protocol the PI has developed (135). Urine samples will be pre-screened for cotinine with 1-Step Rapid Nicotine test for both groups at times 1 and 2. At Microgen, we will obtain quantitative results by ELISA for urine cotinine. We have focused on testing the hormones at time 1 and time 2 only as our previous results justify these critical time periods for the neuroendocrine response. We will follow the World Health Organization's Good Laboratory Practices (136).

Infant outcomes. Pregnancy duration will be recorded in completed weeks and days and birthweight in grams. We will collect data on any NICU admissions. In Ruiz-R01-NR07891, we collected data on ~200 babies without difficulty from Dr Chavez's delivery records. These data will include diagnoses for the infant, especially those linked to pregnancy complications. We will collect data on medically indicated PTB versus spontaneous PTB and early term births (37-39 weeks) and will use gestational age as a continuous variable as longer gestation, even among term infants, benefits both cognitive and motor development (137). **Infant sex as a covariate of biological and infant outcomes.** Evidence indicates that male infant outcomes may be more affected by prenatal adversities than female infant outcomes (138), including a link between maternal prenatal depression and impaired neonatal motor behavior in male infants (139) and a link between prenatal maternal depression and increased anxiety seen in females (140).

15.2 SAFETY ASSESSMENTS

Please see section 9.9 for detailed discussion of safety assessments and protections.

15.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.3.1 DEFINITION OF ADVERSE EVENTS

Adverse Event: Any unfavorable and unintended sign associated with the MLI, regardless of whether it is considered related to the intervention. These include such things as revelations of child abuse, domestic violence. Adverse events also include "unanticipated problems" of any nature (e.g., psychological or social harm) and will be designated as unrelated, related, probably related, or possible related (see below).

15.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse event: Any adverse event that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or results in a congenital anomaly or birth defect. Examples include suicidal attempts, homicidal attempts, drug overdoses.

15.3.3 CLASSIFICATION OF AN ADVERSE EVENT

15.3.3.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Life-threatening event: Any adverse event in which the subject is at immediate risk of death from the reaction as it occurs. This does not include a reaction that, if it were to occur in a more serious form, might cause death. Although unlikely for this behavioral intervention, an example of this might be a severe allergic reaction during data collection or while participating in the group sessions.

Unexpected event: Any adverse event that is not identified in nature, severity, or frequency in the investigator brochure, study protocol, consent form; or the event was more serious than anticipated. An example of an unexpected event would be a participant falling.

15.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Definitely Related: An adverse event that has a timely relationship to the administration of the investigational study procedure and follows a known pattern of response for which no alternative cause is present.

Probably Related: An adverse event that has a timely relationship to the administration of the investigational study procedure and follows a known pattern of response, but for which a potential alternative cause may be present.

Possibly Related: An adverse event that has a timely relationship to the administration of the investigational study procedure and follows no known pattern of response, but a potential alternative cause does not exist.

Unrelated: An adverse event for which there is evidence that it is definitely related to a cause other than the study procedure; in general no timely relationship to the administration of the procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

15.3.3.3 EXPECTEDNESS

An AE or suspected adverse reaction is considered "unexpected" if it is unlikely to occur in the study population, or it is unlikely to occur at the severity that has been observed.
Dr Christopher Fagundes, a professor of psychology, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

15.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during data collection visits, during a group session for participants of the MLI group, or during a prenatal care visit with the physician.

All AEs, not otherwise precluded per the protocol, will be captured on the Adverse Event Reporting Form as delineated in this section. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The CRC or CRA will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 42 days (length of group sessions) (for SAEs) after the last day of study participation. At each data collection visit for the UC group, the CRA will inquire about the occurrence of AE/SAEs. For the UC Group, events will be followed for outcome information by Dr Chavez until resolution or stabilization. The NP or CNM will follow up with a MLI group member privately after a group session weekly, or as needed, for AEs. The following are the Adverse Event Reporting Forms for the study:

Participant ID # _____

Name: _____

Date: _____

Phone: _____

1. Reason for follow up on site after a session:

Verbal admission of <u>child abuse</u> during group session. (unsolicited response if present)

Time period: _____

NP discussed with participant. (enter summary of discussion)

Follow up:

____ Participant was notified of need for further follow up with child protective services
____ Documentation of referral (include who made the call, date and time of the call, who was contacted, and brief summary of information relayed):

3. Reason for follow up on-site after a session:

2. Verbal admission of <u>domestic violence</u> during group session. (unsolicited)

Time period: _____

Discussed with participant: (enter summary)

Follow up:
_____Participant was given resource list
_____Safety plan was generated
_____Participant refused assistance at this time

3.. Reason for followup on site either after a group session or after a data collection session:

Unsolicited comments that indicate an actual or potential adverse event (generally).

Discussed with participant (enter summary)

Follow up:

15.3.5 ADVERSE EVENT REPORTING

<u>ADVERSE EVENT REPORTING</u>:

Serious adverse events will be reported to the IRB and DSMB within 48 hours days of learning of the event. Unexpected adverse events that are not serious, but may be associated with the intervention, will be reported to the IRB and NIH no later than 30 days after the event on an annual basis. After considering the symptoms, a decision will be made by the PI in conjunction with the DSMB, if indicated, whether to make the recommendation that the participant stop the intervention and/or refer the participant for further evaluation. The PI is responsible for reporting adverse events to the DSMB within 48 hours of the occurrence. The DSMB will determine whether said events are related to the study. All adverse events, serious and non-serious, will be fully documented on the appropriate Adverse Event (AE) Reporting Form. For each adverse event, the investigator will provide the onset, duration, intensity, treatment, required, outcome and action taken. Serious adverse events are not expected to occur during this study.

15.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, the CRC will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the Institutional Review Board (IRB) at Microgen as soon as possible. This reporting should be no later than 10 working days after the investigator first learns of the event.

15.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

15.3.8 EVENTS OF SPECIAL INTEREST

N/A

15.3.9 REPORTING OF PREGNANCY

N/A all participants are pregnant.

15.4 UNANTICIPATED PROBLEMS

15.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated Problems include problem situations that arise during the course of a study but are not directly related to study procedures.

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

These UPs may include loss of data or data collection documents and psychological distress related to the intervention or control condition (as described above).

15.4.2 UNANTICIPATED PROBLEMS REPORTING

A research team member will report any unanticipated problems (UPs) to the Data Coordinating Center (DCC) (in this case Dr Northrup at UT Houston) and to the principal investigator (PI) Dr Ruiz, who will report to the reviewing Institutional Review Board (IRB) (Microgen).The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMB/study sponsor/funding agency within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMB/study sponsor/funding agency within 14 days of the investigator becoming aware of the problem
- All UPs will be reported to appropriate institutional officials, the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator]

15.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

16 STATISTICAL CONSIDERATIONS

16.1 STATISTICAL HYPOTHESES

Primary Endpoints to Test Efficacy:

- **Hypothesis 1a:** Participants in the 6-week MLI will have decreased depressive symptoms, anxiety, and stress, disengaged coping, and increased active coping compared to UC at end-of-treatment and after 6 weeks.
- **Hypothesis 1b:** The effects of MLI versus UC on depression, anxiety, stress, acculturative stress, and coping will be mediated via psychological flexibility and acculturation.

Secondary Endpoints to Test Biological Mechanisms of Efficacy and Health Outcome of Infants:

- **Hypothesis 2a:** Compared to UC, MLI participants will have significantly lower mean levels of CRH over time from baseline to end-of-treatment.
- **Hypothesis 2b**: Compared to UC, MLI participants will have significantly higher progesterone levels and lower estriol levels (higher progesterone/estriol ratios) over time from baseline to end-of-treatment.
- **Hypothesis 3:** As compared to UC, infants from mothers in the MLI group will have longer gestational age, greater birth weight, and fewer NICU admissions.

16.2 SAMPLE SIZE DETERMINATION

Table 1. **Power to detect given effect sizes assuming different rates of attrition.**

Sample Size	15% Attrition *N* = 200 (100/group)			20% Attrition *N* = 190 (95/group)			25% Attrition *N* = 180 (90/group)		
Power	81.1%	86.3%	91.6%	78.8%	84.5%	90.6%	75.4%	82.6%	88.6%
Effect Size	0.300	0.325	0.350	0.300	0.325	0.350	0.300	0.325	0.350

This study is powered for the primary hypothesis in Aim 1 and calculated using k = 1000 Monte Carlo simulations under different conditions in SAS 9.4. Specifically, power estimates focus on

the detection of a statistically significant interaction between time and treatment group in generalized linear mixed models (GLMM). Table 1 describes power to detect effect sizes as small as those shown given the following: (1) a range of plausible attrition rates (~15%, ~20%, and ~25%) (2) a recruited sample size of N = 234 women, (2) a correlation of r = .50 between consecutive observations (baseline to week 6, week 6 to week 12), (3) a correlation of r = .05 for all observations collected at the same time point, and (4) $\alpha = .05/5 = 0.01$, assuming the Bonferroni correction to be conservative across each of the five outcomes described in Hypothesis 1. In practice, the statistical significance will rely on the false discovery rate (FDR) to adjust for multiplicity; this will rely on the observed p values. The powered effect sizes above align with those found in previous research and pilot studies. Our pilot study (n=15) showed an effect size on anxiety that ranged from d = -.37 to d = -1.5; for depression, the effect size ranged from d = -.45 to d = -.76. Our results align with other studies using ACT. McCracken (108) used the PHQ-9 in a RCT (n=73) to measure depression pre- and post-treatment after ACT for chronic pain and found a Cohens d = 0.58. Majumdar (102) found a medium effect for group ACT (η^2 = .07, or d = 0.55).

16.3 POPULATIONS FOR ANALYSES

Intent-to-treat analyses using SAS v. 9.4 and R v.3.6 programs will be conducted. We will investigate any missing data to ascertain if data are missing at random. As each of the proposed analyses can fully incorporate unbalanced data, we will use all collected data even if there is missing data for some of the repeated measures. Missing data will be handled via maximum likelihood, explicit modeling of missingness, and/or multiple imputations as appropriate, each of which is robust to data missing at random. We will investigate the sensitivity of analyses to patterns of missing data. Multiplicity (i.e., multiple comparisons) within families of tests will be addressed via false discovery rate (FDR).

16.4 STATISTICAL ANALYSES

16.4.1 GENERAL APPROACH

All variables will be summarized via descriptive statistics. Categorical data will be summarized by frequency and percent, and continuous data will be summarized in terms of central tendency (i.e., mean/median) and dispersion (i.e., standard deviation). Inferential tests will rely on the statistical significance criterion α =.05 (two-tailed). Hypothesis tests that find values $p \leq .05$ will be considered statistically significant. Covariates may potentially be included in statistical models; details of covariate inclusion are described below in Section 9.4.2. Modeling assumptions will be evaluated via inspection of residual plots and formal statistical tests. Violations of assumptions will be addressed as needed via by transformation, robust estimation coefficient scaling, stratification, or model respecification. Any hypothesis tests that are unable to satisfy statistical modeling assumptions will be reevaluated via equivalent non-parametric tests if possible.

16.4.2 ANALYSIS OF THE PRIMARY ENDPOINTS

Analyses will primarily rely on generalized linear mixed modeling (GLMM) to evaluate the relationships between predictors and outcomes. This flexible approach allows modeling normally or non-normally distributed outcomes (specified by distribution family and link function),

longitudinal or multilevel data (via inclusion of level-2 terms for participant id), and/or nonlinear effects (via inclusion of spline or polynomial terms). The measurement scales for all study outcomes are described above in Section 8.1.

Longitudinal analyses will model each outcome as a function of the treatment group, time, and interaction between the treatment group and time. If the interaction term is not statistically significant, the model will be reduced to main effects only. Follow-up tests of simple effects will evaluate changes in each outcome over time within treatment groups. Cross-sectional models at each time point will use GLMM to model each outcome as a function of the treatment group. In all models, other types of multilevel data (e.g., participants within groups) will utilize a random intercept for group assignment.

Interaction effects will be described as significant or non-significant. If significant, results then focus on simple effects of time within each group; if non-significant, results focus on models of main effects without the interaction. These results will be presented as parameter estimates with 95% confidence intervals for all models that only measure main effects or within-group models of simple effects in the presence of a significant interaction. Graphical presentation will provide a plot of estimated marginal means of outcomes over time by group.

Single and multiple mediator models will investigate the indirect effects of treatment separately on 6-week follow-up measures of depression, anxiety, stress, and coping via intervening (end-of-treatment) measures of psychological flexibility and acculturation. Mediation analyses will rely on Structural Equation Modeling/Path Analysis using MPlus (v. 8.4) to evaluate direct and indirect effects of treatment on outcomes. In the context of the direct effects of treatment, mediational modeling permits estimates of the indirect effects via intervening variables using the product coefficient method. Ninety-five percent confidence intervals will be constructed using a bootstrap resampling approach.

Prior to hypothesis testing, we will inspect relationships between baseline and demographic variables, treatment groups, and outcomes using GLMM. Baseline/demographic covariates demonstrating a relationship with both predictors and outcomes meet criteria as potential confounders and will result in two models, one with and another without covariate adjustment. If inferences are impacted via adjustment, we report both models; otherwise, we will report the less complex model (141, 142).

Some specific covariates to be examined as potential confounders include age, pre-pregnancy body mass index, gravidity, positive cotinine, positive drug screens, fetal sex, group climate scores for MLI sessions, concurrent behavioral therapy, acculturation scores, country of birth, presence or absence of a social security number, SSRI or progesterone use, obstetrical variables (i.e., preeclampsia, gestational diabetes, history of preterm birth, vaginal or systemic infections during the periods between/during data collection and delivery), and frequency of intervention attendance. For the MLI group, number and type (phone for missed sessions only vs. in-person) of sessions will be investigated as moderating (i.e., interacting) dose-response effects of treatment.

Assumptions of statistical modeling and missing data considerations will be addressed as described in Section 9.4.1. With respect to multiplicity, the a priori defined outcomes will be

evaluated at the α = 0.05 significance level. False discovery rate correction for Type I error will be applied to any follow-up or post hoc tests.

16.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The analytic details provided in Section 9.4.2. also apply to any endpoints that may be established *post hoc*.

16.4.4 SAFETY ANALYSES

N/A

16.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

16.4.6 PLANNED INTERIM ANALYSES

N/A

16.4.7 SUB-GROUP ANALYSES

If a given baseline characteristic is determined to influence the relationship between predictors and outcomes via the criteria for confounding described above, that characteristic will also be evaluated as a potential moderator of the time x treatment interaction; in essence providing a three-way interaction. Subgroup analyses will then evaluate the primary statistical models within each group, sample size permitting (model convergence may be an issue if group sizes end up being too small).

16.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

We do not plan to tabulate individual participant data.

16.4.9 EXPLORATORY ANALYSES

N/A

17 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

17.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

17.1.1 INFORMED CONSENT PROCESS

17.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol:

a. Consent form to participate in the study
b. HIPPA form to release prenatal record and birth record

a. CONSENT FORM TO TAKE PART IN RESEARCH

Title: Reductions in Biopsychosocial Risks for Pregnant Latinas and Their Infants: The Mastery Lifestyle Intervention

Protocol Number: H-Ruiz001

Sponsor: National Institutes of Health and Department of Health and Human Services

Principal Investigator: Roberta Jeanne Ruiz, Ph.D., WHCNP-BC, FAAN, Microgen Laboratories LLC, 903 Texas Avenue, La Marque, Texas 77568 USA

Study-Related

Phone Number(s): 713-383-7020

You are being asked to take part in a research study. A Clinical Research Associate (CRA) or the Clinical Research Coordinator (CRC) will go over this consent with you. Your participation is completely voluntary.

18 WHY IS THIS RESEARCH BEING DONE?

The purpose of this study is to determine the helpfulness of group counseling to reduce risks for you and your baby. These risks are related to stress, anxiety and depression (how you feel). The group counseling is called, “the Mastery Lifestyle Intervention” (MLI). The potential for improved emotional health by being in the MLI group may lower the risk for preterm births. The MLI group will be facilitated by a nurse practitioner, a licensed advanced practice nurse, who will be able to address anxieties or problems related to your pregnancy and your mental health.

The MLI group will meet once weekly for six weeks to help you with how you feel and to improve coping. About 234 women will take part in this research.

What are the potential benefits to taking part in this study?

The following benefits were demonstrated in early work by pregnant women who participated:

- Improved coping

- Decreased stress, depression, and anxiety symptoms
- Improved relationships with their partner
- Improved sleep

19 HOW LONG WILL I BE IN THIS RESEARCH?

- For the usual care group, there are 4 visits for data collection 3 of which may take about 1 to 1-1/2 hours each, and one about 20 minutes, for a total of 4 ½ hrs, until 32-36 weeks of your pregnancy.
- For the MLI group, there are 6 visits that may take about 1-1.5 hrs. each, for a total of 6-9 hrs. for group sessions and 4 1/2 hours for data collection until 32-36 weeks of your pregnancy.

What will happen if I take part in this study?

- You will sign the consent form
- You will be placed into the MLI group (plus usual prenatal care) or just receive usual prenatal care by the flip of a coin (50-50 chance).
- Regardless of which group you are in; you will be given several questionnaires about how you feel and how you handle change. You will need to fill out all the questionnaires four different times during your pregnancy and it will take about 90 minutes or less each time. You may skip any questions you do not want to answer on the questionnaires.
- You will have your blood drawn and give saliva and urine samples initially and when you are 20-26 weeks pregnant.
- You will have a fourth data collection visit six weeks after your second data collection, 32-36 weeks of pregnancy, for questionnaires only, and no blood or urine collection, no matter which group you are in.
- After you have your baby, we will look at your medical record to check for any problems you or the baby might have had at birth.
- MLI sessions will be videotaped to ensure quality and to confirm that the NP is running the session effectively. Recordings will be reviewed by members of the research team who are trained to review recordings and may include experts located at other research facilities also involved in this research. Recordings will be identified by number only and your name will not be noted by the study staff or reviewer on any recordings. All study recordings will be kept in locked file cabinets and/or password protected computers with only study staff having access to them. Information from the recordings may be published or shared in study reports as a group to help describe the sessions and how they were conducted, but your name or other data that might reveal who you are will not be revealed in any reports or writings that may result from this study.

20 WILL IT COST ME MONEY, OR WILL I BE PAID FOR TAKING PART IN THIS RESEARCH?

Participation should not cost you any money, only time. We will provide reimbursement for parking costs and for the extra time you are at the prenatal office. You will receive money after data collection visits, even if you do not complete the entire study, no matter which group you are in.

- $40 after completing your first data collection (14-20 weeks of pregnancy), $20 at midpoint after completing the 2 additional questionnaires, $60 at the third data collection visit, and $60 at the fourth and final data collection visit (32-36 weeks of pregnancy).
- If you miss your visit, the CRA will contact you and potentially make a home visit if you cannot come to the office. The CRA will provide you with money after data collections are complete.
- You will also get parking reimbursement for MLI group sessions held in Dr Chavez's office.

21 WHAT OTHER CHOICES DO I HAVE BESIDES TAKING PART IN THIS RESEARCH?

There may be choices to taking part in the study. For example, you may consult with your physician and ask for a referral to a licensed therapist. Another option is to continue with your usual care without being in this study.

Who will see the research and medical records data?

- Representatives of Microgen LLC, UTHealth, NIH, or companies engaged with Microgen to commercialize the MLI. You will not share in any profit that could come from future use of the MLI.

22 COULD BEING IN THIS RESEARCH HURT ME?

23 FOR THE MLI GROUP:

- There is a risk that the MLI may not be as good as current therapy for anxiety, depression or stress.
- There is also a risk that you could have some discomfort from taking part in the MLI group because sensitive emotions or problems may be revealed. To decrease this risk, we have a list of resources we can give you should you have excessive discomfort.
- Your privacy is important and your participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed. You will be assigned a study number with your name protected.
- At the first MLI session, we will talk about the rules in order to lower the risk of your being in the study and keep your privacy. **
- **Exceptions to the confidentiality rule include: 1) if you reveal child or elder abuse, the session leaders are required by law to report that to child or adult protective services; and 2) if you indicate suicidal or homicidal thoughts, we may disclose this information to protect you or others in accordance with Texas law.

Discomforts **for either group** associated with this research include:

- There is a small risk of mild pain or discomfort, bruising and swelling from your blood draw at the puncture site. It is possible that you might have dizziness or fainting. There is a small risk of infection. We will apply pressure with a sterile gauze to avoid bruising and infection and help you to avoid fainting.
- You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.
- You may have mild emotional discomfort from answering the surveys.
- There is a small risk of a loss of confidentiality. We will work hard to keep your confidentiality. We will do our best to maintain your privacy throughout your time in the study.

This research should not harm your pregnancy in any way.

24 WHO CAN ANSWER MY QUESTIONS ABOUT THIS RESEARCH?

If you have questions about the study, please call Dr. Ruiz at 713-383-7020. You can contact the study team at 713-383-7435 (Anna Estrada CRC) or 713-330-9311 (Irma Pecina) to ask questions, discuss problems, or report injuries. If you have questions about your rights, please call Dr. Stowe at 409-935-6700.

25 WHAT IF I AM INJURED BECAUSE OF TAKING PART IN THIS RESEARCH?

If you have an injury as a result of taking part in this research study, no free treatment has been arranged. Also, no other payment has been arranged. However, emergency treatment and professional services are available to you. You should call Dr. Ruiz at the study phone number to tell her of your injury. You will not give up any of your legal rights by signing this consent form.

26 WHAT HAPPENS IF I AGREE TO BE IN THIS RESEARCH, BUT I CHANGE MY MIND LATER?

If you stop being in this study, the information already collected about you and your baby will still be used. We will not collect any more information without your permission. We will notify you of any new information.

A decision either way will not change the services available to you. You may withdraw your permission for us to use your data that has already been collected (other than data needed to keep track of your withdrawal).

27 STATEMENT OF CONSENT:

Your signature documents your consent to take part in this research.

Signature of adult subject capable of consent	Date
Signature of person obtaining consent	Date

b. HIPAA Privacy Authorization Form Microgen Laboratories, LLC

**Authorization for Use or Disclosure of Protected Health Information (Required by the Health Insurance Portability and Accountability Act, 45 C.F.R. Parts 160 and 164) **

NAME OF PARTICIPANT:_____

DATE OF BIRTH_____

1. I give permission for Dr Anthony Chavez, MD (my obstetrical healthcare provider) to use and disclose (share) the protected health information described below to Roberta Jeanne Ruiz, PhD, WHCNP-BC, FAAN, Primary Investigator of this research project.

2. This authorization for release of information covers the period of healthcare from June 2021 to June 2026.

3. I authorize the release of my prenatal health record (including records relating to mental healthcare, communicable diseases, HIV or AIDS, and treatment of alcohol or drug abuse).

4. This authorization shall be in effect until the end of the research study, June 2026, at which time this authorization expires.

5. I understand that I have the right to revoke (cancel) this authorization in writing at any time. I understand that revocation (cancellation) is not effective if any person or entity has already acted, relying upon this authorization.

6. I understand that my treatment, payment, enrollment, or eligibility for benefits will not be controlled by whether or not I sign this authorization.

6. I understand that the health information used in this research study as a result of this authorization may no longer be protected by federal or state law.

Printed Name of Subject	Signature of Subject	Date Time

Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date Time

27.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Our plans for recruitment and consent were informed by results of our pilot work.

- Dr. Chavez will give each potential first trimester participant a brochure and ask if she would like to speak to the on-site study personnel. They will introduce the study to the patients during their first trimester prenatal appointment by giving them a flyer and then encouraging a discussion with the study's Clinical Research Associate (CRA), Ms. Pecina, at the office to determine interest. If there is no study representative at the office when there is a prospective participant, a flyer with the contact phone number for the study will be provided by the office staff.
- The CRA, Ms. Pecina, will be housed at the provider's obstetrical office allowing for recruitment on the heaviest days for the practice when the new obstetrical or return obstetrical patients are seen.
- We will place flyers and posters as informational materials in the office and the restrooms.
- Dr. Chavez will provide a private office for discussion of the study, for determination of eligibility, and to gain informed consent.
- Dr. Chavez has partnered with the research team and agreed that the CRA (Ms. Pecina), CRC, or other study personnel who are appropriately trained in human subjects' protection will be present in the prenatal office to discuss participation in the study with potential participants.
- We will also ask participants to sign a Personal Health Information HIPPA) release to examine their medical records. Dr. Chavez will also allow study personnel (e.g., NP) to collect data from the enrolled participants' prenatal records (after participants have consented) that are relevant to the medical confounders to be controlled for in the study. The NP will collect data from the prenatal records and the birth records and will be able to link the participant's release to their study identification number for data entry purposes.
- The CRA is fluent in Spanish and English and will present recruitment and consent materials in Spanish to Spanish speakers only, if needed.

Processes for Each Group.

The private practice office will serve as a place to host group sessions when the risk of COVID-19 is low enough to allow in person sessions. Until the risk of contracting COVID-19 is minimal, the group sessions will be given over the phone via ZOOM technology. One group will run at a time, either the MLI or UC. Groups will run for 6 weeks with MLI sessions lasting about 90 minutes. A separate Zoom session will be conducted in Spanish with a fluent Spanish speaking NP throughout the entire time for the research as there are a much smaller group of Spanish speakers and it would be difficult to integrate them with the English speakers. The first and last

session (Sessions 1 and 6) will require an additional 1.25 hours of time to accommodate completion of study questionnaires and biologic data collection (blood, urine). For the UC, the second data collection will require about 1.25 hours for data collection. The final data collection for both groups will require less time as there will be no biological measures collected, so about an hour of time.

The providers' office has comfortable chairs and available paid parking. Sessions will start at 14-20 weeks gestation and continue through 20-26 weeks gestation. A 14-20-week window will avoid women who may miscarry yet will be early enough in the 2nd trimester to enhance the probability of expected outcomes. Each session will be led by a NP facilitator with the same NP conducting all sessions for each group. In order to keep the NP blinded as to outcomes, the NP not facilitating the sessions will data collect from the prenatal chart and from the hospital delivery record.

Ms. Pecina, the CRA, will data collect at Sessions 1 and 6 and the CRC will perform venipuncture, test urine specimens. THE CRA will transport samples to Microgen laboratories for storage. The same process for biologic samples and questionnaire data collection will be followed for both groups. As much as possible, we will hold all sessions at the same time of day throughout the study to control for diurnal variability. Ms. Pecina will be trained by the PI in the collection and safe storage/transport of biological samples. All specimens will be transported to Microgen laboratories within 24 hours of collection. To avoid biased results, Ms. Pecina will administer questionnaires using an electronic tablet device but will not participate directly with the groups. The questionnaires will be completed in a private room in the office to avoid the effect of social expectations on responses. We will clarify questions only, not discuss answers. To avoid bias, the NP that is not the group facilitator will collect data from the prenatal chart. For infant health data, the NP will enter delivery data from the hospital charts directly onto the tablet devices with access to the secure database. The same process for biological samples and questionnaire data collection will be followed for both groups.

27.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, NICHD, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Microgen Institutional Review Board (IRB), and NICHD and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met.
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

27.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on a shared drive at UT Health. The PI and Co-Is will be able to log and access the data. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Texas at Houston Medical Branch Department of Community Medicine research staff (Dr Thomas Northrup and Dr Robert Suchting) will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Microgen Laboratories.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

27.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored on a shared drive by the University of Texas at Houston Medical Branch Department of Community Medicine. After the study is

completed, the de-identified, archived data will be transmitted to and stored at Microgen Laboratories, for use by other researchers including those outside of the study.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at Microgen Laboratories. These samples could be used to research the causes of premature birth, its complications and other conditions for which individuals with reactivated viruses such as Epstein Barr Virus and Cytomegalovirus are at potential increased risk, and to improve treatment. Microgen Laboratories will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio sample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through Microgen Laboratories.

27.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Roberta Jeanne Ruiz, PhD, Senior Clinical Health Research Scientist	*Raymond Stowe, PhD, Committee Chairman of the IRB*
Microgen Laboratories, LLC	*Microgen Laboratories, LLC*
903 Texas Avenue La Marque, TX	*903 Texas Avenue La Marque Tx*
409-935-6700	*409=935-6700*
jruiz@microgenlabs.com	*rpstowe@microgenlabs.com*

Direct Report	**Team Member**	**Responsibilities**
NIH	PI Ruiz	Oversight of all team members and training for human subjects including but not limited to: rigor with data collection; fidelity of the intervention; ensure use of decision algorithm for referral of women reporting violence or depression; Ensure attainment of milestones; and overall quality of investigation
Pi Ruiz	Co-I Stotts; Co-I Villarreal	Oversee MLI groups for effectiveness and any problems; Manage participants with homicidal/suicidal intentions or domestic violence

PI Ruiz; Co-I Stotts	Co-I Villarreal	Lead MLI training for NP; fidelity checks for MLI in collaboration with Dr Stotts
PI Ruiz	Co-I Stowe	Oversee analysis of laboratory tests for blood and urine-ensuring quality results, Supervise laboratory technician and safe laboratory practices
Co-I Stowe	Laboratory Technician	Organize and store biological samples, Conduct ELISA analysis of progesterone, estriol and cotinine; Conduct CRH analysis
PI Ruiz	CRC (CRC)	Assists Dr Ruiz in operationalization of the aims by: overseeing immediate data and sample collection with the CRA, assuring planning of groups with CRA after randomization, assists NPs with supplies and needed preparation for groups sessions; tracks incentives, monies used for mileage, parking and taxis; Monitors budget with PI, monitors a weekly report of recruitment and retention of participants
PI Ruiz & CRC (CRC)	CRA Pecina	Recruitment; Informed Consent; Assign each patient with unique de-identified ID number; Data collection for questionnaires; venipuncture and collection of urine samples; Assist in setting up group sessions; Sample preparation and transport to lab; Assist with solving transportation problems and home visits for data collection if needed
PI Ruiz; Co-I Stotts	Co-I Northrup; Co-I Suchting	Set-up database (Northrup) in collaboration with statistician (Suchting); distribute randomization envelopes to CRA; monitor missing data; Review data with team for accuracy and completeness; Prepare IRB application and monitor for any adverse events
PI Ruiz	Co-I Pickler	Setup data collection for nuances related to infant outcomes; Review infant health data monthly after participants start delivering
PI Ruiz	NPs	Conduct group sessions for the intervention either electronically or in person.

27.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB)/Safety Monitoring Committee (SMC) composed of individuals with the appropriate

expertise, including a research scientist in psychology, a board-certified obstetrician, and a professor who has expertise in data management and analysis. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NICHD.

27.1.7 CLINICAL MONITORING

The PI will monitor data accuracy and quality on the shared drive at the minimum every other week, as well as monitoring the training for all the staff, especially the first three months. The PI will verify data with the data manager, Dr Northrup, comprehensively.

27.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Our Co-Investigators will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.
Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents vis electronic tablets (see **Section 27.1.9, Data Handling and Record Keeping**) that will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 13.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations is deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

27.1.9 DATA HANDLING AND RECORD KEEPING

27.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the CRA, the NP Interventionist and the CRC at the clinical obstetrical site. The PI will be responsible for ensuring the accuracy, completeness,

legibility, and timeliness of the data reported in conjunction with the Dr Thomas Northrup, co-Investigator.

All source documents will be completed in a neat, legible manner (i.e., consent forms, HIPPA forms) to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.
Clinical data (including adverse events (AEs), and expected adverse reactions data) and clinical laboratory data will be entered into an Excel database to a data capture system provided by the University of Texas at Houston Medical Center Department of Community Medicine. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

27.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 7 years after the last approval of a marketing application in an International Council on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

27.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the PI to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation. All deviations will be addressed in study source documents, reported to NICHD Program Official and the University of Texas at Houston Medical Center Department of Community Medicine. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The PI will be responsible for knowing and adhering to the reviewing IRB requirements.

Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 10 years after the completion of the primary endpoint by contacting Dr Ruiz, PI. Considerations for ensuring confidentiality of these shared data are described in Section 27.1.3.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

27.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NICHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

27.2 ADDITIONAL CONSIDERATIONS

N/A

27.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations

CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

27.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2	8-11-21	Updated Consent and minor edits	Most current consent is needed for the protocol

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