Prenatal Mindfulness & Hypertension Study

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SUMMARY OF RESEARCH PLAN

Summary and Significance

Hypertensive disorders of pregnancy, defined as a group of diseases including preeclampsia, eclampsia, gestational hypertension, and chronic hypertension, are one of the greatest causes of perinatal morbidity and mortality (ACOG 2013). Consequences of hypertensive disorders of pregnancy include placental abruption, intrauterine growth restriction, seizures, and maternal and infant death. These conditions affect 6-10% of all pregnancies, and the rate has increased substantially over the past several decades (James and Nelson-Piercy 2004, Kintiraki, Papakatsika et al. 2015). Rates of recurrence of hypertensive disorders in subsequent pregnancies may be as high as 94%, depending on the type, timing, and severity of hypertension in prior pregnancies (Hjartardottir, Leifsson et al. 2006).

Once hypertensive disorders develop, treatments are limited to watchful waiting, antihypertensive medications, or ultimately, early delivery. Antihypertensive medications may cause drowsiness, risk for postpartum depression, and intrauterine growth restriction (James and Nelson-Piercy 2004). Thus, initiating antihypertensive medications for mild-moderate hypertension in pregnancy (≥140/90 mmHg) is controversial as the maternal benefits may not outweigh fetal risks (Scantlebury, Schwartz et al. 2013). Despite the devastating consequences of hypertensive disorders in pregnancy and the negative side effects of antihypertensive medications, there are currently no alternatives to pharmacological interventions to prevent hypertension recurrence in pregnancy. Thus, non-pharmacological approaches to prevent recurrence are sorely needed.

Mindfulness interventions hold great potential to prevent recurrence in pregnant women with a history of hypertensive disorders of pregnancy. Results from previous RCTs conducted in other populations show that mindfulness interventions are significantly more effective at reducing blood pressure in patients with pre-hypertension (Hughes, Fresco et al. 2013) and hypertension (Nejati, Zahiroddin et al. 2015) than other stress management interventions (e.g., yoga, progressive muscle relaxation). The evidence is more limited among pregnant samples. There is some evidence that higher mindfulness skills are associated with lower blood pressure in healthy pregnant women (Braeken, Jones et al. 2017). However, traditional mindfulness training (MT) interventions, requiring 2.5 hours of class attendance for 8 weeks plus a full-day retreat, may be difficult to adhere to in pregnancies complicated by hypertensive disorders due to the possible need for activity restriction, hospitalization, increased maternal and fetal monitoring, and home and child care responsibilities. Phone-delivered MT may provide a feasible and effective alternative to traditional class-based MT interventions. Our group has successfully developed and tested a phone-delivered MT intervention among medically complex patients, including pregnant women at risk for preterm birth. The goal of the current study is to determine if phone-delivered MT is feasible and acceptable among pregnant women with histories of hypertensive disorders of pregnancy.

In this exploratory clinical trial we will randomize 30 pregnant women at risk for hypertensive disorders to an 8-week phone-delivered MT intervention (N=15) or treatment as usual (N=15). All women will undergo 24-hour ambulatory blood pressure monitoring before and after the intervention. Our interdisciplinary team is uniquely positioned to execute the proposed study given our complementary expertise in mindfulness interventions, perinatal mental health, and obstetric medicine.

The specific aims of the study are:

Specific Aim 1: To test feasibility and acceptability of phone-delivered mindfulness training for pregnant women with a history of hypertensive disorders of pregnancy. 30 pregnant women with a history of hypertensive disorders of pregnancy will be recruited and randomly assigned to MT (N=15) or to treatment as usual (N=15). Primary outcomes are feasibility and acceptability (>75% attend at least 4 sessions; > 20 on the client satisfaction questionnaire). We will explore preliminary effects (not powered for efficacy) of group differences in ambulatory blood pressure (average daytime, nighttime, and diurnal systolic, diastolic blood pressure, hyperbaric index, blood pressure variability, and dipping status). We will also examine rates of hypertensive disorder recurrence that will be fully tested in a future fully-powered RCT.

Specific Aim 2: Conduct a qualitative analysis of feasibility and acceptability of phone-delivered mindfulness training for pregnant women with a history of hypertensive disorders of pregnancy. Following the mindfulness intervention, we will conduct individual qualitative interviews to solicit feedback on participants' treatment satisfaction, motivation for

participation, barriers and challenges to participation, and appropriateness of the session content for hypertension in pregnancy. Information gained in the qualitative analysis will be used to improve feasibility and acceptability in the future fully-powered RCT.

Specific Aim 3: To examine differences in pathophysiological mechanisms of hypertensive disorders of pregnancy among women receiving mindfulness training vs. usual care. We hypothesize that pregnant women receiving mindfulness training will display reduced inflammation, improved uterine perfusion and fetal growth, and reduced blood pressure, and these mechanisms will in turn reduce risk for hypertensive disorder recurrence.

Anticipated Outcomes. Results from this developmental clinical trial will 1) provide evidence on the feasibility and acceptability of delivering phone-delivered mindfulness training for pregnant women at risk for hypertensive disorders, 2) evaluate if a preliminary signal of change in maternal blood pressure is detected between groups, 3) evaluate if a preliminary signal of change in pathophysiological mechanisms of hypertensive disorders of pregnancy is detected over the course of the study, and 4) solicit feedback from participants on how to improve the feasibility and acceptability of the intervention in future trials. These results will be used to inform a future fully-powered RCT. The results of this line of research are significant because MT could serve as an effective non-pharmacological preventive intervention for hypertensive disorders. Effective preventive interventions hold great promise to reduce the burden of disease to individuals and society.

Research Design & Methods

Phase 1: Recruit Participants and Pilot the Developmental RCT. Participant recruitment for this study will leverage the established infrastructure at the Women's Medicine Collaborative Research Department. The Research Department has 4 research assistants who currently recruit participants for ongoing perinatal studies at OBGYN offices throughout Rhode Island that service over 5,000 pregnant patients/year. Given that approximately 300 of these pregnant women will have a history of hypertensive disorders of pregnancy, and we aim to recruit 10% of these women for the current study, we are confident that we will be able to enroll N=30 pregnant women at risk for hypertensive disorders of pregnancy for this study. The rationale for recruiting pregnant women at risk for hypertensive disorders is based on the high rate of recurrence of hypertensive disorders in subsequent pregnancies (Zhang, Troendle et al. 2000), the high degree of diagnostic overlap among these conditions, and the common medical interventions that women with these conditions typically receive.

Participants assigned to the MT intervention will receive 30-minute phone-delivered MT sessions once a week for 8 weeks. Dr. Elena Salmoirago-Blotcher, a faculty member in the Brown Center for Mindfulness, a certified mindfulness instructor, and an expert in mind-body approaches for cardiovascular health, developed this intervention. The MT intervention is based upon the curriculum of the Mindfulness-Based Stress Reduction program (including practices such as awareness of breath, awareness of body sensations ("body scan"), awareness of sounds, emotions, and thoughts, open awareness, as well as cultivating mindfulness throughout daily activities). Participants will be asked to practice the mindfulness exercises for 15 minutes a day using audio recordings developed by our group. Our team has successfully delivered this intervention in a sample of pregnant women at risk for preterm delivery.

Phase 2: Quantitative Evaluation of Feasibility and Acceptability. Measures of feasibility will include recruitment and retention rates, as well as adherence to the intervention. Specifically, we will measure the number of participants screened and eligible to participate, the number and reasons for refusal, the number and reason for dropout, and the number lost to follow-up. We will also measure the number of MT sessions attended and the minutes spent listening to the guided mindfulness practice recordings. The study will be considered feasible if > 75% of participants complete $\geq$ 4 sessions and practice mindfulness exercises for 15 minutes a day for $\geq$ 4 days a week. Acceptability will be measured using the Client satisfaction Questionnaire (CSQ-8 (Larsen, Attkisson et al. 1979)). Scores on the CTQ-8range from 8-32. The study will be considered acceptable if > 75% of participants report a score of $\geq$ 20.

SUSPENDED DURING COVID19 PANDEMIC. Secondary Outcome Measurement. Blood pressure will be assessed using *ambulatory blood pressure monitoring* (ABPM, ScottCare device). This validated device (Zawadzki, Vandekar et al. 2013) can measure BP every 30 minutes for 24 hours. ScottCare

software automatically scores blood pressure readings to calculate average daytime, nighttime, and diurnal systolic, and diastolic blood pressure, hyperbaric index, blood pressure variability, and dipping status (BP fall > 10% from daytime levels). Prior research demonstrates high sensitivity and specificity of ABPM (specifically the hyperbaric index, an index of BP load on organs, blood pressure variability, and dipping status) in the early detection of hypertension. Peripheral blood will be collected via venipuncture before and after the 8-week mindfulness or treatment as usual interval. Samples will be de-identified and stored for future research purposes. (Participants will consent to the collection and banking of blood using a separate consent form.) Research ultrasonography assessments will also be performed before and after the 8-week mindfulness intervention or treatment as usual. The collection of maternal and fetal ultrasound findings will allow evaluation of maternal uterine artery Doppler parameters, placenta size, fetal growth velocity rate and fetal Doppler parameters among the two study groups. Diagnoses of hypertensive disorders will be collected via medical chart review and rates of recurrence will be compared across groups. We will conduct linear mixed effects models to evaluate changes in blood pressure (dependent variable) according to time, group, and time x group interaction (independent variables).

Phase 3: Qualitative Evaluation of Feasibility and Acceptability. Following the intervention, women will be asked to complete in-depth qualitative interviews to solicit feedback on the intervention. Feedback from qualitative interviews will be used to identify patterns and themes in participants' responses that will then be used to further tailor and refine the phone-delivered MT intervention for pregnant women with histories of hypertensive disorders of pregnancy in preparation for a future fully-powered RCT.

Recruitment. A sample of 30 pregnant women, ages 18-40, before 20 weeks' gestation will be recruited into the study. Pregnant women from OBGYN clinics and practices will be recruited through identification of eligible women through chart review. Women will also be recruited through placements of posters and brochures. Other recruitment sites are: hospital websites, various community sites and community groups, community health care groups and community-based newspapers. Interested participants will be contacted by study staff andinitial screening will take place by telephone.

Inclusion/Exclusion Criteria

Inclusion/exclusion criteria: ≥ 18 years old, singleton pregnancy, English speaking, <20 weeks' gestation at enrollment, history of a hypertensive disorder, and no current engagement in mindfulness training (defined as weekly yoga, mindfulness exercises (including on-line), or meditation). Women will be asked to complete a baseline visit remotely to obtain background information on maternal characteristics and medical conditions in pregnancy. Following the baseline session, women will be randomized to phone-delivered MT intervention or to treatment as usual. Randomization will be stratified based on antihypertensive medication use (yes/no), if necessary.

Procedures

Initial Telephone Screening. Interested pregnant women will complete a telephone screen including questions to assess inclusion/exclusion criteria. Visit 1 will then be scheduled with interested participants who meet initial inclusion criteria.

Baseline Assessment: NO IN-PERSON RESEARCH ACTIVITIES WILL TAKE PLACE DURING THE COVID19 PANDEMIC. Interested and eligible participants from the phone screen will be invited to complete the Baseline Assessment by telephone or video call. The first session will take place remotely by telephone or video call and will include informed consent, interview, and self-report questionnaire measures. The electronic consent procedure and questionnaires will be performed by using Redcap platform, through Lifespan. Paper-forms will always remain an option for every participant. All the remote research interactions will be completed by using institutionally approved secure video conferencing, phone calls and secure Redcap based platform. A link to the electronic consent form, or the paper form, will be e-mailed/mailed to a participant prior to the phone/video visit. The consent can then be returned by mail, by email, or in person at a later date. **During the COVID19 pandemic, participants will complete questionnaires remotely via paper (mailed in advance of session) and/or via REDCap survey.**

Following consent, participants will complete the interview portion of the session. We will also ask participants the best way to leave messages for them. In addition, we will obtain information regarding two "locators," or friends or family members who will know how to reach the participant. If the interviews indicate that the participant is ineligible for continuation in the study, the session may be terminated at that point in time. Women who endorse severe depressive symptoms or psychosis will not be eligible to complete the mindfulness intervention, and referrals will be provided. Severe depression or psychosis will be defined as the following: Edinburgh Postpartum Depression Scale score of >25 indicates severe depression and "threshold" score on one re more on items 1-5 of psychosis screen indicates current psychosis. The ineligible participants will receive full compensation for the session. This initial interview session will last approximately 1 hour. Participants will receive $50 for completing the interviews and self-reports.

Ambulatory Blood Pressure Monitoring. **SUSPENDED DURING COVID19 PANDEMIC.** Following the baseline visit, all eligible and enrolled participants will be instructed to complete ambulatory blood pressure monitoring for 24 hours. Blood pressure will be assessed using *ambulatory blood pressure monitoring* (ABPM, ScottCare device). This validated device (Zawadzki, Vandekar et al. 2013) can measure BP every 30 minutes for 24 hours. ScottCare software automatically scores blood pressure readings to calculate average daytime, nighttime, and diurnal systolic, and diastolic blood pressure, hyperbaric index, blood pressure variability, and dipping status (BP fall > 10% from daytime levels). Participants will be paid $50 for completing blood pressure monitoring.

Peripheral blood draw and specimen banking. **SUSPENDED DURING COVID19 PANDEMIC.** Before randomization, women will be asked to provide a peripheral blood sample for specimen banking. We will make every effort to time the peripheral blood draw with clinical blood draws in order to minimize participant burden. Participants who consent to specimen collection and banking will have 10mL (< 1 tablespoon) of blood collected via venipuncture at Lifespan Laboratories. Blood samples will be identified only by the participant ID and stored at -80° C at the RISE building (TMH) for later analysis. Participants will not receive the results of the blood draw. This information is included in the informed consent form.

Research Ultrasound. **SUSPENDED DURING COVID19 PANDEMIC.** We will make every effort to time the research ultrasound with clinical ultrasounds in order to minimize participant burden. The first research ultrasound before randomization will occur with, or after, participants have their clinical anatomy scan. Before each research ultrasound, participants will be read a "script" that emphasizes that research ultrasounds do not take the place of clinical ultrasounds. For research ultrasounds, participants will be placed on the ultrasound bed onto their back in a semi-recumbent position, slightly tilted toward their left side. For the research studies, we will use ultrasound devices currently in use for clinical evaluations. We will record fetal heart rate, fetal position, placental position and size, and amniotic fluid index according to standard clinical protocols. Next, we will record fetal biometric parameters and Doppler measurements of maternal and fetal blood vessels. If the following abnormal findings are detected on the research ultrasound, the OB/GYN provider will be notified: 1) fetal anomalies, 2) estimated fetal weight below 10%, 3) abnormal umbilical blood flow, 4) abnormal levels of amniotic fluid, and 5) absent fetal heart rate. Participants will not receive the results of the research ultrasounds. This information is included in the informed consent form.

Randomization. All participants will receive usual prenatal care, which may include intervention to prevent or treat hypertension during gestation. Following the completion of the baseline session, participants will be randomized to treatment group (mindfulness training + treatment as usual, or treatment as usual) using a stratified randomization approach (stratified by hypertension medication use).

Mindfulness Training Intervention + Treatment as Usual. Interested and eligible participants from the Baseline Assessment will be invited to take part in an 8-week phone-delivered mindfulness intervention, in addition to continuing to attend usual prenatal care appointments. Each intervention session will last approximately 30 minutes (4 hours of total intervention) and will be scheduled for a time that is convenient for the participant. Mindfulness training sessions will occur once per week. Sessions

will be led by an experienced mindfulness instructor, and participants will have the same instructor throughout the intervention. The 30 minutes will include 20 minutes of intervention and 10 minutes for addressing participants' questions and scheduling subsequent sessions. Mindfulness training modules will include awareness of breath, body scan meditation, and sitting and movement meditations. Women will be provided with recordings of mindfulness exercises to use for practice between sessions. Women will be asked to practice mindfulness activities daily in between sessions. Women will be provided with audiotapes that will guide their mindfulness exercises. We will ask that women practice for 15 minutes each day, and record the date and duration of their practice. With participant permission, intervention sessions will be audiotaped for the purpose of assessing treatment fidelity. A research assistant will contact the participant between sessions to ask about any problem or discomfort participants might be experiencing during and between the training sessions, as well as to ask about any problem or difficulty they are having attending prenatal care appointments.

Treatment as Usual. Participants randomized to the treatment as usual condition will continue to receive their regularly-scheduled prenatal care, which may include interventions to prevent or treatment hypertension during pregnancy. A research assistant will check in with the participant each week to ask if they have been to any prenatal care appointments, and if so, the number and length of time spent at each.

Repeat Ambulatory Blood Pressure Monitoring. SUSPENDED DURING COVID19 PANDEMIC. All participants will repeat the 24-hour blood pressure monitoring after approximately 8 weeks from enrollment or following completion of the mindfulness intervention, if applicable. The procedures for ambulatory blood pressure monitoring are identical to those that were completed prior to randomization (see above). Participants will be paid $50 for completing blood pressure monitoring.

Follow-up Visit. **NO IN-PERSON RESEARCH ACTIVITIES WILL TAKE PLACE DURING THE COVID19 PANDEMIC.** At the follow-up visit we will ask women to complete same self-report measures that were completed at the Baseline Assessment. **During the COVID19 pandemic, participants will complete questionnaires remotely via paper (mailed in advance) and/or REDCap.** We will also obtain updated information about participants' health throughout the pregnancy, including emerging medical conditions and new medications ("Pregnancy Context_ Follow-Up"). At the final session, women will be asked to provide feedback about the intervention in individual interviews. Interviews include open questions and learn directly from our participants' experience. In particular, at the follow-up assessment we will ask women about their overall satisfaction with the program, the acceptability of the length of sessions, the frequency of sessions, the number of sessions, and the content of sessions. This interview session will last approximately 1 hour. Participants will be compensated $50 for their time.

Peripheral blood draw and specimen banking. SUSPENDED DURING COVID19 PANDEMIC. After the 8-week mindfulness training + usual care, or usual care only intervals, women will be asked to provide a peripheral blood sample for specimen banking. Participants who consent to specimen collection and banking will have 10mL (< 1 tablespoon) of blood collected via venipuncture at Lifespan Laboratories. Blood samples will be identified only by the participant ID and stored at -80° C at the RISE building (TMH) for later analysis.

Research Ultrasound. SUSPENDED DURING COVID19 PANDEMIC. After the 8-week mindfulness training + usual care or usual care only intervals, research ultrasound procedures identical to those prior to randomization will be performed. We will again make every effort to time the research ultrasounds to coincide with clinical ultrasounds. We will only perform a follow-up research ultrasound that does not coincide with a clinical ultrasound if the clinical ultrasound is scheduled at a time when the mindfulness intervention is still underway, or if the clinical ultrasound is scheduled for greater than 3 weeks after the end of the mindfulness intervention. This is necessary to insure the integrity of the research data and to test the aims of the study.

Measures

Pregnancy Context. The Pregnancy Context interview assesses current pregnancy health status, the number and gestational birth age of previous pregnancies, the number of previous deliveries, current and

past pregnancy-specific problems (i.e., gestational diabetes, cervical insufficiency), maternal infection, and medications in pregnancy, socioeconomic status, and previous experience with mindfulness and/or stress management interventions. Pregnancy Context Follow-Up: At the follow-up visit participants will be asked to provide updated information on their pregnancy including new diagnoses and medications. Health Behaviors: Women will provide information on weekly cigarette and alcohol use by completing the Timeline Follow-back Interview (Sobell and Sobell 1992). Preeclampsia symptom screen: Participants will be asked to report if they have experienced symptoms of preeclampsia at each study visit and each mindfulness session. Self-Report Measures: Women will be asked to report on past experiences of childhood trauma (MACE) at the baseline session. Women will be asked to complete self-report measures of stress (Perceived Stress Scale), mood (Edinburgh Postnatal Depression Scale, Pregnancy-Specific Anxiety), and Mindfulness (Five Facets of Mindfulness Scale, Multidimensional Assessment of Interoceptive Awareness) at the baseline session and following the intervention. We will also ask women to complete a measure of perceived sleep quality (Pittsburgh Sleep Quality Index), quality of life (Quality of Life Measure), and PCL-5 (PTSD Checklist for DSM-5) at the baseline and follow-up sessions. At the follow-up session we will ask women to provide feedback about the intervention (Intervention Satisfaction Questions). See Table 1 below for a list of measures and timing of administration.

Table 1	**Baseline**	**MT Intervention**	**Follow-up**
Interview Measures			
Pregnancy Context	**X**		
Pregnancy ContextFollow-Up			**X**
Health Behaviors	**X**		**X**
Psychosis Screen	**X**		
Preeclampsia screen	**X**	**X (all visits)**	**X**
Self-Report Measures			
Edinburgh Postnatal Depression Scale	**X**		**X**
Pregnancy-Specific Anxiety	**X**		**X**
Perceived Stress Scale	**X**		**X**
Five Facets of Mindfulness Scale	**X**		**X**
Multidimensional Assessment of Interoceptive Awareness (MAIA)	**X**		**X**
Pittsburgh Sleep Quality Index	**X**		**X**
Maltreatment and Abuse Chronology of Exposure (MACE)	**X**		
Quality of Life Measure	**X**		**X**
PTSD Checklist for DSM-5	**X**		**X**
Intervention satisfaction questionnaire			**X**
Qualitative Interview Questions			**X**
Ambulatory Blood Pressure Monitoring SUSPENEDED DURING PANDEMIC			
In-laboratory blood pressure	**X**		**X**
24-hour blood pressure monitoring	**X**		**X**
Blood draw	**X**		**X**
Research Ultrasound	**X**		**X**

Pregnancy Outcome Measures

Following delivery we will collect outcomes of the pregnancy including diagnoses of hypertension, preeclampsia, and eclampsia. We will also record incidence of spontaneous preterm labor, elective and medically-indicated labor induction, infant birth weight, APGAR scores, length of time in the NICU, and gestational age at birth via medical record following birth. Women will be asked to complete a release of information in order for medical records to be provided to the study. Data will be extracted from medical records, entered into de-identified datasets, and then destroyed.

Human Subjects

We will enroll 30 pregnant women at risk for hypertensive disorders of pregnancy in the current study. No restrictions will be placed on enrollment by race or ethnicity.

Sources of Materials. All data collection will follow HIPAA guidelines. Data will be collected directly from participants and from medical charts by the research assistant. Data will include participant responses to interviews, paper-and-pencil questionnaires, and blood pressure data. We will assess eligibility criteria from phone interviews. All data will be treated as confidential and will never be stored or reported in association with identifying information. Only the PI and RA will have access to identifiable information. Both the PI and RA will have completed training in the ethical conduct of research prior to participant enrollment.

Potential Risks

SUSPENDED DURING COVID19 PANDEMIC. Detection of elevated blood pressure during in-laboratory or ambulatory blood pressure monitoring. Elevated blood pressure readings may be detected during blood pressure assessments.
Detection of symptoms consistent with preeclampsia. Symptoms of preeclampsia may be reported at study visits or at mindfulness sessions.
Confidentiality or loss of privacy. We will collect potentially sensitive information about participants; if released inappropriately, participants may experience embarrassment or distress.
Embarrassment from interview or self-report measures. There is the possibility that mothers may feel uncomfortable by some of the interview questions and self-report measures.
Risk of discovering symptoms consistent with a psychiatric disorder. Because we are asking women to complete questionnaires regarding depression and anxiety symptoms, we may be more likely to discover a psychological disorder (depression).
Risk of discovering current domestic violence or abuse. Participants may disclose current domestic violence or abuse when completing the trauma questionnaire.
SUSPENDED DURING COVID19 PANDEMIC. Risk of venipuncture. There may be discomfort associated with obtaining peripheral blood via venipuncture. Venipuncture also carries the risk of developing a hematoma at the site of the puncture and a <1% risk of developing an infection at the site of puncture.
SUSPENDED DURING COVID19 PANDEMIC. Detection of incidental fetal abnormal findings. Indices of abnormal fetal growth may be detected at ultrasound sessions.
SUSPENDED DURING COVID19 PANDEMIC. Risk of research ultrasound. Ultrasound imaging is based on mechanical sound waves (non-ionizing radiation) so it doesn't have the same risks as X-rays or other types of imaging systems such as MRI. Ultrasound imaging is generally considered safe when used prudently by appropriately trained health care providers. Ultrasound energy does have the potential to heat tissues slightly or produce small pockets of gas in body fluids/tissues and corresponding bioeffects have been described in animal models. No bioeffects have been reported in humans or in human fetuses, however, when exposures are be kept as low as reasonably achievable (ALARA).

Adequacy of Protection against Risks

SUSPENDED DURING COVID19 PANDEMIC. Discovery of elevated blood pressure. If elevated blood pressure readings (> 140/90) are recorded during in-laboratory or ambulatory blood pressure monitoring, the participant's prenatal care provider will be notified immediately after the study team is aware of the elevated reading(s). If blood pressure measurements are 160/110 or higher, participants will be instructed to go to the emergency room. Participants would also be instructed to go to the emergency room if the ob/gyn provider advises it. Participants will be aware that elevated blood pressure readings will be communicated to their prenatal care provider. This information is included in the informed consent form.

Detection of symptoms consistent with preeclampsia. Women will be asked to report on symptoms of preeclampsia at each study visit as well as at each phone-delivered mindfulness session. If a participant endorses PEC symptoms, their provider will be immediately notified by phone. The trained research assistant and mindfulness instructor will indicate that they are calling on behalf of the

participant due to a medical emergency. The participant will also be instructed to call their provider. If neither the participant nor the research staff are able to speak with a provider, the participant will be instructed to go to an emergency room for evaluation.

Recruitment and Informed Consent. Written informed consent (including a description of the nature, purpose, risks, and benefits of the study) will be obtained from individuals who express interest in participating. Participants will also provide release of information from medical records for the purpose of determining birth outcomes following delivery. The voluntary nature of the study and the participant's right to withdrawal at any time will be emphasized during the consent process; this information will be provided to participants in written form at the time of consent.

Embarrassment from interview or self-report measures: To ease any potential discomfort, the research staff will be trained to interview in a comfortable non-judgmental manner. Additionally, women will have the option to stop the interview at any time, or to decline to complete any of the self-report measures. Finally, the PI will be available should any discomfort not be alleviated during or after the interview/self-report.

Risk of discovering symptoms consistent with a psychiatric disorder: Because we are asking women to report on symptoms of depression and anxiety, we may be more likely to discover a psychological disorder. For all participants who endorse elevated symptoms of depression or anxiety, the RA or Dr. Bublitz will provide referrals and information regarding treatment options. We will also send a note to the participant's OBGYN to inform them of the patient's elevated symptoms. In the event that a study participant endorses suicidal ideation, the interviewer will complete a lethality assessment, will consult with Dr. Bublitz to formulate a course of action, and will consult with the participant's care provider. Appropriate intervention or follow-up care will be arranged with the treating clinician or, if hospitalization is required, through emergency services. If real risk of harm to self or others is identified, we will remain with the participant until an emergency intervention can be planned and implemented. Standard procedures include explaining (and re-explaining) all upcoming procedures to participants and conveying a strong attitude of caring, flexibility, and individualized attention to participant. Should a subject ask to discontinue participation, or should staff detect an elevated level of distress, ongoing procedures will be halted immediately and a decision will be made in conjunction with the PI regarding the subject's ability to continue in the protocol. Subjects are reminded throughout the course of the study that they are free to terminate their participation at any time.

Risk of discovering current domestic violence or abuse. If participants report current domestic violence or abuse, they will be provided with information on follow up testing and medical care (see brochure from Day One). They will be encouraged to contact Day One in Providence Rhode Island, an organization that provides treatment, intervention, education, advocacy, and prevention services to Rhode Islanders of all ages. They can call the Day One 24-hour help line at 1-800-494-8100, or the National Sexual Assault Hotline at 1-800-656-4673.

SUSPENDED DURING COVID19 PANDEMIC. Risk of venipuncture. Blood draws will be coordinated, when possible, with blood draws obtained during routine medical care to minimize the number of times venipuncture is performed. Venipuncture will be performed via standard techniques and skin preparation (with alcohol) to minimize the risks of developing a hematoma or infection at the site of puncture. A topical anesthetic will be made available for use prior to venipuncture if desired. Venipuncture will be performed by a phlebotomist, physician or nurse experienced in drawing blood to minimize risk of discomfort. **Risk of detection of abnormal fetal parameters.** Measurements of fetal growth and vascular parameters will be collected at research ultrasound sessions. If the following abnormal findings are detected on the research ultrasound, we will alert the OB/GYN provider: 1) fetal anomalies, 2) estimated fetal weight below 10%, 3) abnormal umbilical blood flow, 4) abnormal levels of amniotic fluid, and 5) absent fetal heart rate. The prenatal care provider who will then determine whether follow up with a clinical ultrasound is needed. Ultrasound and Doppler studies are routine clinical tests with no significant risks attached to them (Bhide, Acharya et al. 2013). Moreover, assessment of uterine and umbilical artery by Doppler techniques are recommended and defined as essential research variables for studies on hypertensive disorders of pregnancy and fetal growth restriction, by international research committees (Khalil, Gordijn et al. 2019, Myatt, Redman et al. 2014), as research standard and non-invasive

method to evaluate placenta function. The reason is that abnormalities of the placenta and abnormal blood flow of the placental vessels usually occur before clinical onset of preeclampsia and fetal growth restriction (Baschat 2011, Velauthar, Plana et al. 2014). Normal reference ranges of fetal and maternal arterial Doppler parameters have been published, including normal reference ranges of maternal uterine artery from 11 to 41 weeks' gestation (Baschat and Gembruch 2003, Brown, Di Luzio et al. 1998, Gomez, Figueras et al. 2008).

For the research studies, we will use ultrasound devices currently in use for clinical evaluations. Per national and international guidelines (Bhide, Acharya et al. 2013, Holt and Abramowicz 2017), when performing Doppler, mechanical (MI) and thermal (TI) indices will be displayed on the ultrasound screen. We will maintain T1 ≤ 1 and the exposure time will be kept as short as possible (Bhide, Acharya et al. 2013). Participants will be positioned on their back, leaning to the left, with a wedge or pillow under the right maternal back to prevent compression of the vena cava.

With respect to *threats to confidentiality and integrity of the data*, the following procedures will be in place:

Confidentiality Safeguards. To minimize any risk of accidental disclosure of confidential information about the project, all work described herein will be conducted with utmost regard to confidentiality. The Women's Medicine Collaborative Research Department, a locked facility where all data entry will take place, has instituted a number of plans to safeguard subject confidentiality. First, all data entry from the experiment will take place directly in our facility. All staff involved with the project will receive training in confidentiality, and will sign a work agreement that states that a breach of confidentiality will be grounds for immediate dismissal. Second, a log of participants will be locked in the PI's research office at the Women's Medicine Collaborative. This log will also be stored on a computer in a password-protected file with access only by authorized personnel. Otherwise, all information obtained from participants will be identified with random research numbers rather than names. All identifying information will be removed from the data file after the subject has completed the study (or dropped out from participation). All data materials will be kept in locked file cabinets in the locked research facility. The study database will be stored on Lifespan computers with access only by authorized personnel. Questionnaires and interview data will be kept in a locked filing cabinet. Consent forms will be stored in a separate locked filing cabinet, and will not be linked with subject numbers. All computers at the research facility are password protected with backup to a secure server. Data analysis will take place on computers at the Women's Medicine Collaborative. All computer files and written reports and papers will not identify subjects or make identification possible. We are confident that these precautions effectively minimize the risk of accidental or willful disclosure of confidential information.

Potential Benefits of the Proposed Research:

Previous research provides supportive evidence that mindfulness interventions may effectively reduce symptoms of depression, anxiety, and stress in pregnant women. Therefore, we believe that one benefit of participating may be that participants who receive mindfulness training could experience fewer symptoms of psychological distress.

Importance of the Knowledge to be Gained:

The results of the proposed study will provide preliminary evidence on the feasibility and acceptability of a phone-delivered mindfulness training intervention for pregnant women at risk for hypertension disorders. Results will also provide evidence on the effectiveness of the intervention at reducing psychological symptoms of distress in pregnancy. Finally, results may provide preliminary evidence on the usefulness of such interventions on reducing rates of hypertension in at-risk women. We expect that these benefits will outweigh potential risks to participants.

Data and Safety Monitoring Plan:

Dr. Bublitz will have primary responsibility for monitoring all participants. Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be immediately brought to the attention of the RIH IRB. Dr. Bublitz will be responsible for completing an Adverse Events Form should an event occur. She will report Serious Adverse Events to the IRB within 24 hours of having received notice of the event. Adverse event reports will be reviewed annually with RIH IRB to ensure participant safety. In the

event that a study participant endorses suicidal ideation during an interview, the interviewer will complete a lethality assessment, will consult with the PI to formulate a course of action, and, with written permission, will consult with the participant's care provider. Appropriate intervention or follow-up care will be arranged with the treating clinician or, if hospitalization is required, through emergency services at Butler, The Miriam, or Rhode Island hospital.

Statistical Approach

Randomization. We will use a stratified randomization procedure to assign participants to mindfulness training vs. usual care based on medications for hypertension. The randomization scheme will be generated based on a permuted block randomization procedure with small random sized blocks. Randomization will be stratified by hypertension medications (yes/no).

Sample size considerations. The proposed sample size was estimated to have sufficient power to assess feasibility and acceptability, as well as to provide a reasonable sample with which to estimate effect sizes and confidence intervals for secondary outcomes. We propose to enroll 30 participants in a 1:1 ratio to mindfulness training and usual care. With a two-sided alpha-level of 0.05, we will have more than sufficient power (>80%) to detect acceptability differences in the small-medium range, d=0.45/w=.2.

Missing data. All analyses will be on the intent-to-treat sample under various assumptions about the missing data mechanism. Sensitivity to these assumptions will be tested.

Blinding. Study staff conducting the baseline and follow-up evaluations will be blinded to women's randomized group assignment. Pathologist examining placental histopathology will be blind to treatment condition.

Treatment Fidelity. Mindfulness training sessions will be audiotaped to assess treatment fidelity. Treatment fidelity checklists for each mindfulness session were previously developed by Dr. Salmoirago-Blotcher and will be used to monitor reliability, validity, and fidelity of the mindfulness training intervention.

INFORMED CONSENT

Lifespan Affiliate Site where research will be conducted

☐ Rhode Island Hospital
☐ Bradley Hospital ☐
☒ The Miriam Hospital
☐ Newport Hospital
☐ Gateway Healthcare

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

015918
Committee #

_____
Name of Study Volunteer

Prenatal mindfulness training for pregnant women at risk for hypertension

You are being asked to take part in a research study. All research studies at Lifespan hospitals follow the rules of the state of Rhode Island, the United States government and Lifespan. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form with the person who explained the study to you. A member of the research team will call you, at your convenience, to review the consent form with you and to answer all the questions you may have, before you decide to sign. This form summarizes the information you discussed. You will be given a copy of this form to keep.

1. Nature and Purpose of the Study

You are being asked to take part in a research project because we are interested in understanding if a phone-delivered mindfulness intervention can be delivered to pregnant women who had problems with their blood pressure in the past. We are also interested in your opinions about this intervention, and your ideas for how to improve it for pregnant women in the future. We expect to enroll 30 pregnant women. The study is sponsored by the Brown Center for Mindfulness, the Cardiopulmonary Vascular Biology COBRE, and the Women's Medicine Collaborative.

2. Explanation of Procedures

If you decide to be part of the study and are selected, you will participate in a study visit in which we will ask you some questions about your pregnancy, your symptoms of psychological stress before and during pregnancy, and your health. Study procedures will be done remotely. This means that you may be asked to complete some interview questions during a phone call or during a video call. You will be asked to complete questionnaires on paper or through an electronic survey. Before starting any remote interaction, a person from the research team will explain to you all the details of the remote interaction, such as type of technology needed and will provide answers to all the questions you may have. For the research remote procedures, the research team will use only the technologies approved by Lifespan IS/IT.

After you complete the first study visit, you will be randomly assigned by chance to participate either in an 8 week phone-delivered mindfulness intervention (in addition to usual prenatal care), or to continue to receive your usual prenatal care. This means you have a 50% chance of

participating in the mindfulness intervention. After about 8 weeks, we will ask you again about your symptoms of psychological stress and health in pregnancy, and we will ask you some questions about your experiences in the study.

If you are eligible to participate after the first visit and are randomized to participate in the mindfulness intervention, we will ask you to take part in 8 phone-delivered individual mindfulness training sessions. These sessions will occur approximately once a week for 8 weeks. Each session will take approximately 30 minutes. Therefore, the total time that you will participate in the mindfulness intervention is about 4 hours. Mindfulness is a type of relaxation exercise that involves paying attention to the present moment. The intervention will be conducted by an experienced Mindfulness instructor. With your permission, we may tape record these phone sessions to help us with coding the intervention; the tapes will be destroyed at the end of the study. Between these phone sessions, we will encourage you to practice the mindfulness exercises everyday on your own time. We will ask you to listen to an audio recording of the mindfulness exercises that you learn in sessions every day for 15 minutes a day. We will ask you to write down the times that you practice these techniques. When you have completed the mindfulness intervention, we will ask you what you liked and disliked about the intervention, your reasons for attending or missing sessions, and your ideas for ways to improve the intervention in the future.

If you are eligible to participate after the first visit and are randomized to the “treatment as usual” study group, we will continue to contact you by phone once a week for 8 weeks while you

receive your usual prenatal care. On these phone calls we will ask you if you have been attending prenatal care appointments.

We will also ask you for your permission to release your medical record following delivery in order to record the outcomes of your pregnancy.

If you report current severe depression or psychosis at the first interview, you will not be eligible to continue in the study. We will provide you with referrals to mental health providers in the community. With your permission, we will also write your OB/GYN provider a letter to let them know about elevated symptoms of depression or psychosis so that they can also help to connect you with additional services.

We will ask you to provide information which will be used to maintain contact with you and also provide information about two "locators," or friends or family members who will know how to reach you in case you cannot be reached.

Compensation:

You will be compensated $50 for the first and final study visits. These interviews will be conducted at the Women's Medicine Collaborative or by phone.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the phone-delivered mindfulness intervention.. Those services will be paid for by the study and will not be billed to you or your health insurance company.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are routine examinations by your OB/GYN provider. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information:

If you have questions about this study, please call Margaret Bublitz, Ph.D. at (401) 793-7884.

3. Discomforts and Risks

In this study you will be asked some questions about your feelings and behaviors. It is possible that some of the questions may make you uncomfortable. All staff members are professional and will not talk to any other people about what you say unless you say you may harm others or yourself. You may skip questions that make you uncomfortable. If you are experiencing elevated symptoms of depression or anxiety you may be referred for additional treatment so you can receive the care you need, or you can request such a referral. With your permission, we will also

write your OB/GYN provider a letter to let them know about elevated symptoms of depression or anxiety so that they can also help to connect you with additional services.

Mindfulness is intended to be a helpful experience, but some patients may find this an uncomfortable experience. Some psychological discomfort, usually mild and transitory, may rarely happen in subjects that do not have severe depression or psychosis. A member of the study staff will contact you weekly to ask you about any problem or discomfort you might be experiencing during and between the training sessions. If you experience any of these symptoms a member of the study staff will provide you with resources for additional treatment. You may stop participating at any time.

4. Benefits

Although you may not benefit directly from participation, by taking part in this study you are helping researchers understand and improve mindfulness interventions for pregnant women. We hope that these interventions may result in improved health for pregnant women in the future.

5. Alternative Therapies

Alternative therapies include individual or group behavioral treatments for depression, anxiety, and stress, and medications. If you are interested in these therapies we are happy to provide referrals. These treatments will not prevent you from participating in this study. You may leave this study at any time.

6. Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

Optional: Follow-up after Withdrawal of Consent

If you leave the study, it would still be useful for us to know how you do for the remainder of your pregnancy and delivery. We would appreciate if you would permit us to get follow-up information about your health from your doctor or your medical record.

____ If I withdraw from the study, you have my permission to collect information about my health from my doctor or medical record.

_____ I do not give my permission for you to continue to collect information about me if I stop participating in the study.

_____	_____
Signature of study volunteer	Date

You have the right to change your mind at any time regarding follow-up after withdrawal. If you decide to quit the study please tell the head researcher Margaret Bublitz, Ph.D. at (401) 793-7884.

7. Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, Lifespan or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, Lifespan might be able to help you pay if you qualify for free care under Lifespan policy. However, Lifespan has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

8. Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of

people who take part in research studies you may contact Janice Muratori in the Lifespan Office of Research Administration, at (401) 444-6246.

9. Confidentiality and Research Authorization for Use and Disclosure of Your Health Care Information

Your research records will be treated as private health care records and will be protected according to Lifespan privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of Lifespan) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor: The Brown Center for Mindfulness, the Cardiopulmonary Vascular Biology COBRE, and the Women's Medicine Collaborative.
- Doctors, nurses, laboratories and others who provide services to you or the sponsor in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights; European Medicines Agency
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.
- Accrediting Organizations

There are times when the law might require or permit Lifespan to release your health information without your permission. For example, Rhode Island law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any Lifespan health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Please initial the following permissions:

_____ **I give permission** to tape record my sessions during the study. The tapes will only be used for coding purposes.

_____ **I do not give permission** to tape record my sessions during the study. The tapes will only be used for coding purposes.

_____ **I give permission** for researchers to contact me in the future for research

purposes.

_____ **I do not give permission** for researchers to contact me in the future for research purposes.

_____ **I give permission** for researchers to contact the "locators" for whom I have provided information in order to contact me for research purposes.

_____ **I do not give permission** for researchers to contact the "locators" for whom I have provided information in order to contact me for research purposes.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the Lifespan Privacy Notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____

Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____

Signature of witness (required if consent Date

is presented orally or at the request of the IRB)

_____ _____

Signature of Translator Date

_____ _____ _____

Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

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