Version #11 07/29/2024

Study Title: Pilot RCT of Remote Mental Health and Substance Use Screening, Brief Intervention and Referral to Treatment (SBIRT), Compared to In-Person SBIRT for Peripartum Women.
Principal Investigator: Constance Guille, MD, MSCR

1.0 Objectives / Specific Aims

Specific Aim 1

The goal of Specific Aim 1 is to develop an effective remote mental health and substance use Screening, Brief Intervention and Referral to Treatment (SBIRT) program for pregnant and postpartum women. The **objectives** of this current application for Specific Aim 1 are to conduct a pilot RCT of a text-message based SBIRT and home-based telemedicine services for pregnant and postpartum women – called Listening to Women (LTW), compared to treatment as usual (TAU) with the primary objective to provide effect size estimates for a larger RCT.

Specific Aim 1: Conduct a pilot, small-scale randomized controlled trial to examine feasibility and preliminary efficacy of LTW, compared to TAU. Outcomes related to feasibility include percentage of eligible patients **recruited**, **study attrition, study retention**, and mental health and substance use treatment appointment **attendance**. Outcomes related to **preliminary efficacy** will include participation in screening, referral and treatment at baseline, compared to TAU.

The central hypotheses for Specific Aim 1 are that the study is feasible and women assigned to LTW will be more likely to screen positive and successfully obtain treatment in less time, compared to those that are assigned to TAU.

Specific Aim 2

Upon completion of Specific Aim 1, the goal of Specific Aim 2 is to evaluate the effectiveness of a remote mental health and substance use Screening, Brief Intervention and Referral to Treatment (SBIRT) program for pregnant and postpartum women. The **objectives** of this current application for Specific Aim 2 are to conduct an RCT of a text-message based SBIRT and home-based telemedicine services for pregnant and postpartum women – called Listening to Women (LTW), compared to treatment as usual (TAU) with the primary objective to include attendance to treatment at baseline, compared to TAU.

Specific Aim 2: Conduct a randomized controlled trial to examine the effectiveness of LTW, compared to TAU. Outcomes related to **effectiveness** include attendance to treatment at baseline, compared to TAU.

The central hypotheses are that a greater proportion of women assigned to LTW will attend treatment following a referral, compared to TAU.

Specific Aim 3

The goal of Specific Aim 3 is to gather data related to maternal and newborn diagnosis codes, health care utilization, and costs for our study participants with Medicaid.

Specific Aim 3: We will compare Medicaid data among those assigned to LTW vs. TAU.

The central hypothesis is that those assigned to LTW will have lower health care utilization and costs during the postpartum year, compared to TAU.

2.0 Background

During pregnancy and the year postpartum (perinatal period), mental health problems are common such as mood, anxiety and substance use disorders. Perinatal mood and anxiety disorders are the most common complication of pregnancy and childbirth affecting at least 1 in 7 perinatal women [1]. Perinatal substance use is also common, and the prevalence is increasing. Perinatal opioid use disorder alone has increased 4-fold over the past decade [2]. Perinatal mental health and substance use are associated with significant maternal, obstetric, infant and child morbidity [3-9], and mortality [10-14].

Given the prevalence and impact of perinatal mood, anxiety and substance use disorders, and evidence demonstrating mitigation of its effects on maternal and child health through psychotherapy and psychopharmacotherapy [16,17], a multitude of professional societies recommend universal screening of pregnant and/or postpartum women using validated screening tools and provision of adequate mental health treatment and/or treatment referrals [18-22]. Unfortunately, however, the vast majority of women with mood, anxiety or substance use problems will remain under-diagnosed and under-treated [23-24]. Less than 50% of peripartum women with a mental illness, and less than 20% of women with a substance use problem are identified in clinical settings [6]. Among these women, less than 15% receive treatment, fewer than 10% receive adequate treatment and less than 5% achieve remission [4].

While mental health screening is widely accepted by perinatal women and Ob/Gyn providers [25,26], further work is needed to facilitate implementation of screenings in Ob/Gyn practices that translate to treatment participation. However, key provider and systems-level barriers to treatment exist and include: 1) lack of screening in obstetric settings and lack of provider training in technical aspects of mental health and substance use disorder care [26-28] and relevant communication skills [29]; 2) absence of standardized processes and procedures for integrated obstetric and mental health and substance use disorder treatment [29,30]; 3) lack of mental health providers willing to treat pregnant women [30]; 4) lack of referral networks [29-33]; and, 5) inadequate capacity and resources to ensure mental health evaluation, treatment, follow-up, and care coordination [29- 35].

To address these barriers we designed, implemented and piloted LTW in routine perinatal care in one obstetric practice (see 3.0 Intervention to be Studied) as part of a quality improvement project. Our pilot demonstrates high rates of participation with 87.78% (273/311) of women approached agreeing to take part in LTW and completing the text-message screening. Preliminary data comparing LTW (N=273) to a historical dataset extracted from the EHR including peripartum women receiving in-person SBIRT in the same clinic (N=2,988) found a significantly greater proportion of women enrolled in LTW screened positive (81.15% vs. 33.33%; X^2=169.50, p<0.0001), were referred for treatment (76.12% vs. 57.63%; X^2=18.03, p<0.0001), and received treatment (94.91% vs. 16.04%; X^2=245.41, p<0.0001), compared to women receiving in-person SBIRT.

While these preliminary data are exciting, a randomized control trial will be necessary to determine the feasibility and efficacy of LTW. The goal of Specific Aim 1 is to examine the feasibility and preliminary efficacy of the proposed RCT methodology. Specific Aim 1 will inform Specific Aim 2 to then conduct a larger-scale RCT that examines LTW, compared to a control condition. This will allow us to identify and address barriers in recruitment, retention, use of LTW, and other procedures essential to successful conduct of the RCT. This approach is consistent with expert recommendations to use pilot mechanisms to test the feasibility of doing a full-scale RCT, use data yielded by the pilot study to "de-bug" the methodology, and to assess optimal strategies to executing the RCT [51- R34].

3.0 Intervention to be studied

LTW is a mobile phone-based program designed to enhance delivery of Screening, Brief Intervention, and Referral to Treatment (SBIRT), an evidence-based approach for mental health and substance use screening

and treatment for perinatal women [36-38]. This program was created as a result of key informant interviews with obstetric providers and pregnant and postpartum women with opioid use disorders. Feedback from these groups informed the development of LTW.

The program utilizes mobile phone text message-based screenings with immediate automated feedback, paired with remote care coordination and, if appropriate, home-based telemedicine mental health and substance use disorder treatment services. Women coming into routine prenatal care (see Recruitment) are eligible to take part in the study. Those agreeing to take part are sent a text message with routine mental health and substance use screening questions (see LTW protocol for screening questions) currently employed as part of standard of care. These screening questions are the SBIRT which is a survey with 9 questions related to depression, anxiety, substance abuse (alcohol, cigarettes, other drugs including prescription medication), and domestic violence (see LTW protocol). However, LTW uses text-message based screening with phone based assessment and referral to treatment, and TAU is an in-person screening and referral to treatment assessment. The same screening tools are used to assess substance abuse and mental health problems in LTW and TAU. Once they complete these screenings via text message, they are provided immediate feedback about their scores, and recommendations (see LTW protocol for automated messages). Contact information for the study's care coordinator is also provided along with her availability i.e., Monday – Friday 8am-5pm. In addition, while specific questions about suicidal ideation are not asked via the text message screening, all participants receive a text message: "If you are ever experiencing a mental health emergency, such as a desire to harm yourself or others, please go to your nearest emergency room. If you are feeling suicidal you can call the National Suicide Prevention Lifeline 1-800-273-8255 anytime" (see LTW protocol for automated messages).

Information about the screening is stored in a REDCap database. A care coordinator is reviewing this information Monday through Friday 8am-5pm and texts or calls any patient that screens positive for mental health or substance use that requires further assessment as would be done in-person during routine clinical care (see LTW protocol describing branching logic from screens and clinical risk categories). The care coordinator contacts the patient and further assesses their mental health and substance use symptoms and needs for resources and/or treatment. If the participant would benefit from further mental health and/or substance use evaluation and treatment, the care coordinator schedules the patient for a home-based telemedicine visit. The care coordinator communicates all screening information in the Electronic Health Record (EHR) for all providers to review, and if applicable includes information about the scheduled appointment or resources provided.

4.0 Study Endpoints

Specific Aim 1:

Primary pilot efficacy outcome variables include:

Completion of SBIRT: We will compare the proportion of participants that complete a screen for mental health and substance use, the proportion of those screening positive that are referred to treatment, and the proportion of those referred to treatment that had at least one mental health and/or substance use disorder treatment appointment among those assigned to LTW, compared to TAU.

Time to Treatment: We will measure the time from completion of screening positive to time of first mental health or substance use treatment appointment (if a referral to treatment was appropriate) among those assigned to LTW, compared to TAU.

Reduction in Mental Health Symptoms: Among women referred for treatment, we will compare the mean change in the Edinburgh Postnatal Depression Scale (EPDS) among those assigned to LTW, compared to TAU. *Of note, the suicidal ideation question (item #10) will be omitted from this questionnaire.*

Reduction in Substance Use: Among women referred for treatment, we will compare change in substance use frequency and amount as measured by the NIDA-Modified Assist (see LTW protocol) among those assigned to LTW, compared to TAU.

Improved Maternal Functioning: Among women referred for treatment, we will compare the change in maternal functioning measured by the Medical Outcomes Study Short Form 36 (SF-36v2) among those assigned to LTW, compared to TAU.

Secondary pilot feasibility and acceptability outcome variables include:

Recruitment: We will determine the proportion of patients who agree to participate as compared to the total number solicited to enroll for each recruitment approach.

Attrition: We will examine the proportion of study participants that prematurely terminate i.e., do not complete screenings, or are unable to be contacted for referral and/or treatment.

Study retention: We will determine the proportion of study participants that complete all assessment points associated with the protocol.

Treatment Attendance: We will collect data from the EHR to determine the proportion of participants that attended a mental health or substance use treatment appointment.

Improved Health-Related Social Needs: Among women referred for treatment, we will compare the change in health-related social needs measured by the Accountable Health Communities (AHC) Health-Related Social Needs (HRSN) Screening Tool among those assigned to LTW, compared to TAU.

Voice Biomarkers: Voice analysis will be completed using an online platform SurveyLex (owned by NeuroLex, Inc.). Among women referred for treatment, we will analyze voice recordings for characteristics (acoustic, linguistic, or meta feature) which may be compared between those assigned to LTW and those assigned to TAU, and compared to other measures collected in either LTW or TAU including EPDS, NIDA Modified Assist, and/or AHC HRSN.

Specific Aim 2:

Primary Outcome:

Attendance to Treatment: treatment attendance (defined as attending at least 1 or more visits with a mental health and/or substance use disorder (SUD) treatment provider during pregnancy and the postpartum year)

Secondary Outcomes

Reduction in Mental Health Symptoms: Among women referred for treatment, we will compare the mean change in the Edinburgh Postnatal Depression Scale (EPDS), GAD-7 Anxiety and CSSRS among those assigned to LTW, compared to TAU. *Of note, the suicidal ideation question (item #10) will be omitted from the EPDS questionnaire.*

Reduction in Substance Use: Among women referred for treatment, we will compare change in substance use frequency and amount as measured by the NIDA-Modified Assist (see LTW protocol) and TLFB among those assigned to LTW, compared to TAU.

Improved Maternal Functioning: Among women referred for treatment, we will compare the change in maternal functioning measured by the Medical Outcomes Study Short Form 36 (SF-36v2) among those assigned to LTW, compared to TAU.

Improved Health-Related Social Needs: Among women referred for treatment, we will compare the change in health-related social needs measured by the Accountable Health Communities (AHC) Health-Related Social Needs (HRSN) Screening Tool among those assigned to LTW, compared to TAU.

For the outcome variables for specific aims 1 and 2 we will collect data from the EHR including SBIRT data, if the participant was referred to treatment, where they were referred to treatment, if they attended a mental health or substance use treatment appointment and where they attended the appointment, how many appointments they attended, and the numbers of days from date of SBIRT completion to date of mental health or substance use treatment appointment.

Specific Aim 3:

The data that will be collected on study participants with Medicaid include:

Number and costs of prenatal care visits

Number and costs of postpartum care visits

Number and costs of hospitalizations during pregnancy and the postpartum year

Number and costs of ED visits during pregnancy and the postpartum year
Number and costs of newborn care visits (outpatient, inpatient and ED) in the first year of life
Maternal diagnosis codes for prenatal care visits, postpartum care visits, hospitalizations and ED visits
Newborn diagnosis codes for outpatient, inpatient and ED visits

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria include: 1) age 18-41; 2) currently pregnant or postpartum; 3) if pregnant, receiving prenatal care; 4) English fluency; 5) owner of a cell phone with SMS text-message based capability; 6) access to WIFI and a device to allow audio and video teleconferencing; 7) able to provide informed consent. Exclusion criteria: None

6.0 Number of Subjects

A total of 450 participants will be randomized in Specific Aim 1 (n=100) and Specific Aim 2 (n=350). To randomize 450 participants we will need to approach about 1,500 participants in order to get to 450 total participants.

7.0 Setting

Recruitment will occur remotely, in person and via the EHR. Potential participants will be pregnant women receiving prenatal care and postpartum women.

8.0 Recruitment Methods

Recruitment will occur remotely, in person and via the EHR. A Research Data Request will be submitted to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The recruitment report will include a search for pregnant and postpartum women. The report will include mrn, age, race, ethnicity, date of prenatal care visit, date of postpartum visit, delivery date, ob/gyn provider name, MyChart account (Yes/No), cell phone number, email address and current ICD-9 or 10 diagnoses. The purpose of the ICD codes will be to ensure we are approaching enough women with substance use disorders, and/or a mood or anxiety disorder diagnoses, and therefore likely to screen positive on either an in-person or text-message SBIRT screening. In addition, ICD codes will be used for urn stratification at randomization. Any patients who have not opted out of being contacted for research will be contacted by phone call or text message and invited to participate. If a cell phone number is not available, the message with a link to a RedCap eligibility survey will be sent via email or MyChart message. The study team will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. Our PI's clinic policy is to ask all patients if they would like to be contacted for research opportunities and if they prefer to be contacted by phone or text message. The vast majority of women prefer to be contacted through a text message. Therefore, we believe cold-contacting patients via text is acceptable for this study. All other patients will be contacted through their providers to be informed of the study if the provider feels it is appropriate. If the potential participant's provider has agreed to have the study team contact their patient, a phone call or text message will be sent to the potential participant inviting them to take part in the study. If a cell phone number is not available, the message with a link to a RedCap eligibility survey will be sent via email. If the potential participant does not respond to the phone call, text or email, the study team may also notify potential participants that a message was sent to them via MyChart. The text message (or email/MyChart message) will include a link to a brief RedCap eligibility survey. For those meeting the eligibility screening criteria, the RA/RC will schedule a time to verify eligibility criteria and review the informed consent either remotely or in-person.

Another method of recruitment will include Women's Health Services clinics, where after women are identified as pregnant or postpartum by the patient's nurse or provider, they will be approached by the study team, with the provider's permission, to take part in the study. Additionally, research staff may do a review of Women's Health Services provider schedules and patient charts in EPIC to identify potentially eligible women for inclusion. Research staff will approach patients when they arrive for their regularly scheduled appointment.

We will also recruit from the MUSC antepartum unit and the mother-baby unit. Patients will be approached by the study team, with the provider's permission, to take part in the study. Additionally, research staff may do a review of the antepartum and mother-baby unit schedules and patient charts in EPIC to identify potentially eligible women for inclusion. Research staff will approach patients while they are staying on the antepartum and mother-baby units. If the patient agrees to taking part in the study the RA will consent the participant and complete baseline procedures.
Another way to recruit is the potentially eligible patients in the PI and Co-Is practices will be informed and approached about the study as the PI and Co-Is feel is appropriate. Participants will also be recruited via study advertisement (e.g., flyers) and online postings (e.g., social media, linkedin).

9.0 Consent Process
Signed informed consent will be obtained from study participants. The consent process will take place via one of the following modalities: 1) Remote or in person electronic consent (e-consent) via REDCap (if remote, e-consent will be facilitated with a discussion over the phone or via video), 2) Remote consent via doxy.me facilitated with either a discussion over the phone or video connection via doxy.me, 3) Mailed (paper) consent facilitated with a discussion over the phone, or 4) in person consent (e.g., in clinic).

All participants will be provided with a hard copy and/or an electronic copy of the consent form. Participants will be informed that participation in this research is strictly voluntary. Informed consent will include a detailed description of the purpose and the procedures of the study emphasizing our policy regarding privacy and confidentiality and an opportunity for the individual to ask any questions or voice concerns. Signatures on the consent form may be obtained with paper and pen OR electronically via REDCap or doxy.me. Participants who do not have access to the required technology to complete consent remotely via REDCap or doxy.me will be given the option to complete consent via mail facilitated with a discussion over the phone.

10.0 Study Design / Methods

Specific aim 1: A two arm pilot RCT (N=100) with 2:1 allocation will examine feasibility and preliminary efficacy of LTW, compared to TAU. Specific aim 2: A RCT (N=350) with 2:1 allocation will examine effectiveness of LTW, compared to TAU. As of the approval of amendment #12 the allocation will switch to 1(LTW):2(TAU) for specific aim 2. Recruitment will primarily occur proactively and remotely via the EHR. We will conduct a weekly EHR search via a recruitment report for all new pregnant and postpartum patients in the past week. The report will include mrn, age, race, ethnicity, date of prenatal care visit, date of postpartum visit, delivery date, ob/gyn provider name, MyChart account (Yes/No), cell phone number, email address and current ICD-9 or 10 diagnoses. Any patients who have not opted out of being contacted for research will be contacted and invited to participate. The study team will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. If the potential participant has not opted out of being contacted, or the potential participant's provider has agreed to have the study team contact their patient, a phone call will be made or message will be sent via text, email or MyChart message to the potential participant inviting them to take part in the study. This invitation will include clear opt out procedures should the patient not wish to be contacted in the future for the purpose of this study. If interested, participants will complete a screening online via REDCap to determine study eligibility (see above for inclusion criteria). After completing preliminary determination of eligibility, if eligible and interested in participating in the study, participants will be scheduled for a time to complete informed consent (see 9.0 Consent Process).

Following consent, all participants will subsequently be text messaged and/or emailed a REDCap link, accessible via smartphone, tablet, or computer to complete study assessments. Assessments that need to be completed by interview will be scheduled with study staff and completed via doxy.me or telephone. For specific aim 1 participants only, participants will also complete voice analysis through Surveylex. Participants will be presented with a questionnaire consisting of one task to complete through the Surveylex online form. One task to be answered and entered as text, and three tasks involving voice recordings in response to prompts. The tasks in the online form include the following: Text question (one task): 1) What is your participant ID?; Voice recording (three tasks): During voice recording tasks, the participant will be reminded that there is no right or

wrong answer for these tasks and that they may choose to skip the question or stop their answer at any time 1) Please repeat this phrase: “The quick brown fox jumped over the lazy dogs.” (10 seconds) 2) Please describe yesterday from start to finish (30 seconds) and 3) Please describe what brings you happiness (30 seconds). Assessments will occur at baseline (following consent). Participants will be randomized to LTW or TAU, respectively.
Survey assessments are estimated to take 30 minutes to complete and will be administered remotely via REDCap through our established procedures and via doxy.me or telephone for interview assessments. Voice analysis for specific aim 1 participants only takes less than 10 minutes to complete and can be completed remotely. Participants will be compensated via electronic gift cards which will be emailed or texted to participants. Participants will receive $25 for completion of the baseline assessments. To encourage participants to complete all 3 surveys, participants will be paid an additional $20 if they complete all 3 surveys (baseline).

Assessments include

Measures	Baseline
Consent	X
Randomization	X
Demographics Questionnaire	X
EPDS Survey	X
NIDA Modified Assist	X
Accountable Health Communities (AHC) Health-Related Social Needs (HRSN) Screening Tool	X
The Medical Outcomes Study Short Form Survey 36 (SF-36v2)	X
*Voice Biomarkers	X
**GAD-7 Anxiety	X
+***Columbia Suicide Severity Rating Scale (CSSRS)	X
+***Timeline Follow-Back (TLFB)	X
***Usability Scale Survey	X

*Only the 100 participants in specific aim 1 complete voice biomarkers
**Only participants in specific aim 2 complete the GAD-7, CSSRS and TLFB
***Only participants assigned to LTW will complete the usability scale
+ As of the approval of amendment 10 newly enrolled participants will not complete CSSRS and TLFB. Participants consented prior to the approval of amendment 10 will complete CSSRS and TLFB at baseline.

Specific aim 3: We will gather healthcare utilization data on our study participants who have Medicaid insurance. The MUSC study team will extract the maternal Medicaid IDs from our study participants with Medicaid insurance from the EHR. We will share a list of these maternal Medicaid IDs with Medicaid, and they will return data related to maternal and newborn diagnosis codes, health care utilization and costs for these participants i.e., prenatal care visits, postpartum care visits, hospitalizations and ED visits during pregnancy and the postpartum year. The MUSC study team will send the maternal Medicaid ID’s of study participants to Medicaid in a password protected spreadsheet. Medicaid will send the MUSC study team a password protected spreadsheet of data. The spreadsheet of data Medicaid will send back to MUSC will be coded since

it will contain the Medicaid ID's of participants.

The Medicaid ID is the only link to subjects in the study. The document linking Medicaid ID's and our study participants will be stored on a University secure network drive or in MUSC BOX. The linking document will be stored separately from the study data and only trained study personnel will have access to the linking document.

Study data will be stored on a University secure network drive or in MUSC BOX. The spreadsheet of data that Medicaid will send the MUSC study team will be password protected. Only trained study personnel will have access to the password protected data spreadsheet.

The MUSC study team will have access to the Medicaid ID's as well as Medicaid.

11.0 Data Management

Data Management

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. The recruitment report project will be housed in RedCap and will only be accessible to the research team. The research team will only have access to the RedCap recruitment project while actively enrolling for the study. The recruitment report will be stored in a separate RedCap project from the project containing our research data.
Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff. Voice sample data gathered through SurveyLex for the participants in specific aim 1 only, is stored by default on NeuroLex's HIPAA compliant Microsoft Azure servers managed by NeuroLex. Access to this data is limited to research staff by a single unique username and password. Voice features collected through Surveylex will be download and stored on an MUSC Box account, accessible only to study staff.

For specific aim 3, the Medicaid ID is the only link to subjects in the study. The document linking Medicaid ID's and our study participants will be stored on a University secure network drive or in MUSC BOX. The linking document will be stored separately from the study data and only trained study personnel will have access to the linking document. Study data will be stored on a University secure network drive or in MUSC BOX. The spreadsheet of data that Medicaid will send the MUSC study team will be password protected. Only trained study personnel will have access to the password protected data spreadsheet. The MUSC study team will have access to the Medicaid ID's as well as Medicaid.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This plan is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (https://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan).

Summary of the Protocol
The goal of this work is to develop an effective remote mental health and substance use Screening, Brief Intervention and Referral to Treatment (SBIRT) program for pregnant and postpartum women. The **objectives** of this current application are 1.) to conduct a pilot RCT of a text-message based SBIRT and home-based telemedicine services for pregnant and postpartum women – called Listening to Women (LTW), compared to treatment as usual (TAU) with the primary objective to provide effect size estimates for a larger RCT and 2.) to conduct a larger scale RCT to examine the effectiveness of LTW, compared to TAU.

Trial Management
The study will be managed from the Women's Reproductive Behavioral Health Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC). Recruitment, data collection, data management, and treatment provision will be coordinated and centrally managed at our research lab at MUSC and will be implemented within local MUSC clinics.

Data Management and Analysis
Participants will enter data in REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). The data analysis plan is outlined above.

Quality Assurance
Accuracy and completeness of the data collected will be ensured by weekly review. The REDCap system does not accept outliers, illogical response patterns, etc. The PI and research assistants will have weekly meetings to discuss any qualitative comments received during data collection and any problems in data collection. The PI will examine the database for potential irregularities monthly. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality procedures are outlined above.

Regulatory Issues
All serious AEs will be reported to the MUSC Committee on Human Research within 48 hrs. Follow-up of all unexpected and serious AEs will also be reported. All AEs will be reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB, and protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be 5% or less. Potential conflicts of interest (COI) will be reported using the SRNT rules for disclosure as well as the rules of MUSC's COI committee.

Trial Safety
<u>Process of AE/SAE collection, assessing by PI and/or medical monitor and reporting</u>

AEs and SAEs occurring during the course of the study will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting training. The PI and study team will identify any potential AEs during the course of the study from subject self-report. This information will be provided to the PI, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE

Adverse events are defined as any untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment. Serious adverse events are defined as any medical occurrence that:

1. Results in death,
2. Is life-threatening,

3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect.

OR

6. Requires intervention to prevent one of the above outcomes

Documentation and Reporting

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information, if available, will be documented in a progress note in the research record as appropriate to allow monitoring and evaluation of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the subject is no longer in the study as stated in the protocol.

When a reportable SAE is identified, the research coordinator will initiate an SAE form, and the following individuals will be notified by facsimile transmission within 24 hours of the site's initial notification of the SAE:

i. The PI will provide oversight, consultation, assessment and documentation as appropriate of the SAE.
ii. The PI will notify the MUSC institutional review board (IRB) and complete the AE report form in conjunction with the study coordinator. The MUSC IRB meets monthly and communication with the IRB is through email, memos, official IRB forms, and online reporting.
iii. The NIDA program officer. Any adverse event will be reported to NIDA in an individual adverse event report.
iv. The data safety monitoring board members

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research coordinator will attach copies of source documents to the SAE report for review by the PI and for forward to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIDA Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the MUSC IRB online as soon as possible, but no later than 10 working days after the PI first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

<u>AE/SAE follow up plan</u>

All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research coordinator. The candidate and the mentorship/consultation team will evaluate the progress of the study at biweekly study team meetings, including periodic assessments of data quality and timeliness, participant recruitment and retention, participant risk versus benefit, and other factors that can affect study outcome. We will also consider factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of participants or the ethics of the study. All AEs are reviewed annually by the Data Safety Monitoring Board (DSMB) and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to NIDA.

Data and Safety Monitoring Plan Administration

The PI will be responsible for monitoring the trial. The PI will examine monthly the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will check weekly with the research assistant about any AEs/SAEs. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

13.0 Risks to Subjects

This is considered a minimal risk study. Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves other than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests. The LTW screening tool is the same tool that is used in clinical practice, the only difference is in its delivery. The potential risks in this study include those related to: a) confidentiality; b) frustration; and c) emotional distress.

a) **Confidentiality**: Participants will be made aware of limits to confidentiality at the beginning of screening and when reviewing study procedures/during informed consent which include report of suicidal or homicidal intent or report of abuse or neglect. If the participant reports substance use during pregnancy or suicidal or homicidal intent or abuse/neglect, Dr. Guille will take appropriate action by completing a psychiatric assessment and facilitating appropriate treatment. Additional appropriate actions as outlined by the MUSC IRB, NIH, and the State of South Carolina, may also include contacting the department of social services, authorities and/or pursuing involuntary commitment at a mental health or substance use disorder treatment facility. If participants present no imminent danger but also need more extensive treatment of mental health or substance use concerns, appropriate care will be facilitated.
b) **Frustration:** Participants may become frustrated while completing study assessments. Participants will be informed that they may refuse to answer any question(s) that they do not wish to answer and that they may discontinue study participation at any time.
c) **Emotional Distress:** Participants will be asked questions that may be sensitive in nature. Participants may find the questions distressing or find the questions make them feel uncomfortable. Participants will be informed that they may refuse to answer any question(s) that they do not wish to answer and that they may discontinue study participation at any time.

Since patients will all currently be receiving prenatal care or will be currently postpartum, there are no additional risks associated with participation in this study.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Study participants will be recruited from local MUSC clinics. Pregnant and postpartum patients identified via the EMR through a recruitment report (research data request) will be sent a message inviting them to participate in a research study. Interested patients will complete determination of eligibility via MUSC's REDCap system, a secure, HIPAA-compliant data management system. All participants will review consent documents and will provide informed consent consistent with procedures outlined above. Participants will be given the opportunity to ask questions about their participation throughout the course of the study. A copy of the informed consent will be kept centrally at our study office within locked filing cabinets, and a copy will be given to each study participant as well. Participants will be given a study phone number and e-mail address to contact for questions.

Protections Against Loss of Confidentiality

All screening information will be kept in a password protected REDCap database. Only key study personnel will have access to the database. If an individual is not eligible to participate based on her answers to the eligibility survey, her screener will not include her name or contact information. Only people who meet eligibility criteria based on the answers to the eligibility survey will be asked if they would like to be contacted about participation in the study and for their name and contact information. Eligible participants' full name, telephone number and

e-mail address will be recorded in the study enrollment log located on a secure MUSC drive or in MUSC Box. The REDCap database and the study enrollment log are the only places where participants' names and subject identification numbers appear together. Eligible participants will be assigned a subject number, will complete informed consent, will be randomized, will complete baseline assessments, and subsequently will receive their randomized intervention.

Upon completing eligibility screening, if study eligible, individuals will be provided with an overview of the study, asked to review study procedures via a consent form, and asked to provide signed consent. Participants will be informed of limitations of confidentiality (i.e., abuse or neglect, intention to harm self or someone else) both verbally and/or in writing during the informed consent process. The consent form will include the participant's name, but not his/her subject number. Consent forms will be provided in English.

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff. Voice sample data gathered through Surveylex for specific aim 1 participants only, will be stored on HIPAA compliant Microsoft Azure servers managed by NeuroLex. MUSC has a BAA in place with Neurolex. MUSC currently pays NeuroLex $100/month for access to their software. MUSC may collect 5000 surveys per month. The data will consist of data tables containing the coded participant ID, date of the recording, voice features, and separates raw voice recording files. Data tables of voice features extracted from the recordings will have only the subject's coded participant ID, and no other identifying information. Access to the SurveyLex account will be limited to research study staff. Staff at NeuroLex will not access this data.
Voice features collected through SurveyLex will be downloaded and stored on an MUSC Box account, accessible only to study staff.

14.0 Potential Benefits to Subjects or Others

There is no direct benefit for subjects from participating in the study.

15.0 Sharing of Results with Subjects

Study enrollment and study outcomes will not be shared with medical staff, including the participant's physician.

References

1. Luca DL, Margiotta C, Staatz C, Garlow E, Christensen A, Zivin K. Financial Toll of Untreated Perinatal Mood and Anxiety Disorders Among 2017 Births in the United States. *Am J Public Health*. 2020;110(6):888-896.

2. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid Use Disorder Documented at Delivery Hospitalization - United States, 1999-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849. Published 2018 Aug 10.

3. Weissman MM. Postpartum Depression and Its Long-term Impact on Children: Many New Questions. *JAMA Psychiatry*. 2018;75(3):227-228.

4. Gentile S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience*. 2017;342:154-166.

5. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry*. 2010;67(10):1012-1024.

6. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry*. 2008;65(7):805-815.

7. Britton HL, Gronwaldt V, Britton JR. Maternal postpartum behaviors and mother-infant relationship during the first year of life. *J Pediatr*. 2001;138(6):905-909.

8. Deave T, Heron J, Evans J, Emond A. The impact of maternal depression in pregnancy on early child development. *BJOG*. 2008;115(8):1043-1051.

9. Paulson JF, Keefe HA, Leiferman JA. Early parental depression and child language development. *J Child Psychol Psychiatry*. 2009;50(3):254-262.

10. Goldman-Mellor S, Margerison CE. Maternal drug-related death and suicide are leading causes of postpartum death in California. *Am J Obstet Gynecol*. 2019;221(5):489.e1-489.e9.

11. Mangla K, Hoffman MC, Trumpff C, O'Grady S, Monk C. Maternal self-harm deaths: An unrecognized and preventable outcome. *Am J Obstet Gynecol*. 2019; 221(4):295-303.

12. Mehta PK, Bachhuber MA, Hoffman R, Srinivas SK. Deaths from unintentional injury, homicide, and suicide during or within 1 year of pregnancy in Philadelphia. *Am J Public Health*. 2016; 106(12):2208-2210. Accessed 11 June 2020.

13. Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal deaths from suicide and overdose in Colorado, 2004-2012. *Obstet Gynecol*. 2016; 128(6):1233-1240. Accessed 11 June 2020

14. Wallace ME, Hoyert D, Williams C, Mendola P. Pregnancy-associated homicide and suicide in 37 US states with enhanced pregnancy surveillance. *Am J Obstet Gynecol*. 2016; 215(3): 364.e1-364.e10.

15. Weissman MM, Pilowsky DJ, Wickramaratne PJ, et al. Remissions in maternal depression and child psychopathology: a STAR*D-child report [published correction appears in JAMA. 2006 Sep 13;296(10):1234]. *JAMA*. 2006;295(12):1389-1398.

16. Beeber LS, Holditch-Davis D, Perreira K, Schwartz TA, Lewis V, Blanchard H, et al. Short-term in-home intervention reduces depressive symptoms in early head start Latina mothers of infants and toddlers. Res Nurs Health. 2010;33(1):60–76.

17. American College of Obstetricians and Gynecologists The American College of Obstetricians and Gynecologists Committee Opinion no. 630. Screening for perinatal depression. Obstetrics and gynecology. 2015;125(5):1268–1271.

18. Kendig S, Keats JP, Hoffman MC, et al. Consensus Bundle on Maternal Mental Health: Perinatal Depression and Anxiety [published correction appears in Obstet Gynecol. 2019 Jun;133(6):1287]. *Obstet Gynecol*. 2017;129(3):422-430.

19. O'Connor E, Rossom RC, Henniger M, Groom HC, Burda BU. Primary care screening for and treatment of depression in pregnant and postpartum women: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016; 315:388–406.

20. A Report from the California Task Force on the Status of Maternal Mental Health Care. April 2017; 1-66.

21. Report of the Task Force to Study Maternal Mental Health, Maryland Senate Bill 74/Chapter 6 (2015). December 2016; 1-78.

22. Smith MV, Shao L, Howell H, Wang H, Poschman K, Yonkers KA. Success of mental health referral among pregnant and postpartum women with psychiatric distress. Gen Hosp Psychiatry. 2009;31(2):155–162.

23. Byatt N, Levin LL, Ziedonis D, Moore Simas TA, Allison J. Enhancing participation in depression Care in Outpatient Perinatal Care Settings: a systematic review. Obstet Gynecol. 2015;126(5):1048–1058.

24. Bauman BL, Ko JY, Cox S, et al. Vital Signs: Postpartum Depressive Symptoms and Provider Discussions About Perinatal Depression - United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(19):575-581. Published 2020 May 15.

25. LaRocco-Cockburn A, Melville J, Bell M, Katon W. Depression screening attitudes and practices among obstetrician-gynecologists. *Obstet Gynecol*. 2003;101(5 Pt 1):892-898.

26. Byatt N, Simas TA, Lundquist RS, Johnson JV, Ziedonis DM. Strategies for improving perinatal depression treatment in north American outpatient obstetric settings. J Psychosom Obstet Gynaecol. 2012;33(4):143–161.

27. Byatt N, Biebel K, Friedman L, Debordes-Jackson G, Ziedonis D, Pbert L. Patient's views on depression care in obstetric settings: how do they compare to the views of perinatal health care professionals? Gen Hosp Psychiatry. 2013;35(6):598–604.

28. Byatt N, Biebel K, Lundquist R, Moore Simas T, Debourdes-Jackson G, Ziedonis D. Patient, provider and system-level barriers and facilitators to addressing perinatal depression. J Reprod. Infant Psychol. 2012;30(5):436–439.

29. Edge D. Falling through the net - black and minority ethnic women and perinatal mental healthcare: health professionals' views. *Gen Hosp Psychiatry*. 2010;32(1):17-25.

30. Palladino CL, Fedock GL, Forman JH, Davis MM, Henshaw E, Flynn HA. OB CARES--the obstetric clinics and resources study: providers' perceptions of addressing perinatal depression--a qualitative study. Gen Hosp Psychiatry. 2011;33(3):267–278.

31. Price SK, Corder-Mabe J, Austin K. Perinatal depression screening and intervention: enhancing health provider involvement. J Women's Health (Larchmt) 2012;21(4):447–455.

32. Kim JJ, La Porte LM, Adams MG, Gordon TE, Kuendig JM, Silver RK. Obstetric care provider engagement in a perinatal depression screening program. Arch Womens Ment Health. 2009;12(3):167–172.

33. Mancini F, Carlson C, Albers L. Use of the postpartum depression screening scale in a collaborative obstetric practice. J Midwifery Womens Health. 2007;52(5):429–434.

34. Byatt N, Biebel K, Debordes-Jackson G, et al. Community mental health provider reluctance to provide pharmacotherapy may be a barrier to addressing perinatal depression: a preliminary study. *Psychiatr Q*. 2013;84(2):169-174.

35. Gjerdingen DK, Yawn BP. Postpartum depression screening: importance, methods, barriers, and recommendations for practice. *J Am Board Fam Med*. 2007;20(3):280-288.

36. Substance Abuse and Mental Health Services Administration (SAMHSA). Screening, brief intervention and referral to treatment (SBIRT) in behavioral healthcare. 2011:1-30.

37. Committee on Obstetric Practice. Committee opinion no. 711: Opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017; 130(2):e81-e94.

38. National Council for Behavioral Health. Center of Excellence for Integrated Health Solutions Web site. https://www.thenationalcouncil.org/integrated-health-coe/. Updated 2020. Accessed June 10, 2020.

39. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol.* 2012;65(3):301-308.