

**Randomized controlled trial of mindfulness-based stress reduction plus prenatal sleep supplement versus usual care: Acceptability, feasibility, and adherence**

**Protocol Number:** Not applicable; this is the first version of the protocol

**National Clinical Trial (NCT) Identified Number:** NCT05017974

**Principal Investigator:** Jennifer Felder, PhD

**Sponsor:** University of California, San Francisco

**Grant Title:** Optimizing a mindfulness-based intervention for poor sleep quality during pregnancy

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## Specific Changes Implemented in Current Version

Description of Change	Brief Rationale
1. Include MBSR classes that are offered at locations in addition to UCSF Osher Center	1. A significant challenge is that the UCSF Osher Center does not offer MBSR frequently, and the classes fill up quickly. Currently, the number of eligible RISE Study participants exceeds the available spots in the Osher MBSR class. Additionally, we have had otherwise eligible study participants who were unable to participate because they were not available at the particular time of the Osher MBSR class
2. Add recruitment sources	2. To enable rapid identification of eligible participants and to maximize likelihood that we can achieve our anticipated accrual rate. We are having a lower yield from our Facebook ads compared to our previous studies. We are adding recruitment sources that we found helpful in previous studies, such as parenting listservs and social media posts
3. Remove Epworth Sleepiness Scale	3. Initially we planned to use the Epworth to screen for narcolepsy. The Epworth has excluded 10% of respondents on our screener. Narcolepsy has a base rate of 0.05%. Thus, it is highly implausible that 10% of respondents had narcolepsy. Instead we believe the Epworth is identifying people with normative pregnancy-related sleepiness. Additionally, this measure is redundant with an item that assesses whether participants have been diagnosed with narcolepsy
4. Increase the gestational age range from 12-28 to 8-28.	4. We have had several potential participants who are experiencing significant sleep disruption, are interested in participating, but are less than 12 weeks pregnant (and will be too far along in their pregnancy for the next available MBSR course). This wider gestational age range is similar to our previous research, in which we evaluated digital CBT for prenatal insomnia, and enrolled participants at any point in pregnancy up until 28 weeks

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## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Center for Complementary and Integrative Health (NCCIH) Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

## INVESTIGATOR'S SIGNATURE

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

Principal Investigator:

Signed:

Date:

\_\_\_\_\_  
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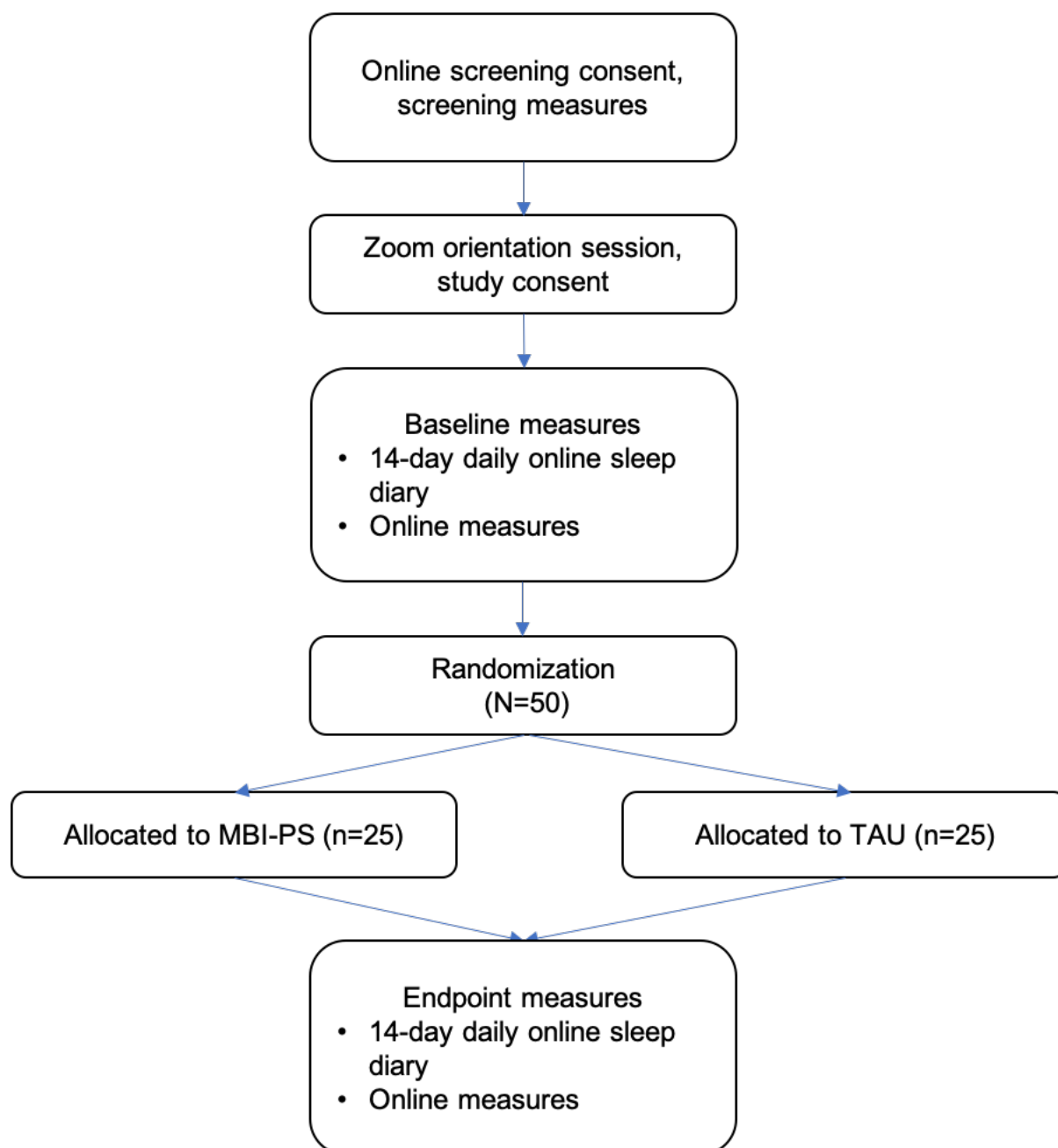
## 1 PROTOCOL SUMMARY

### 1.1 SYNOPSIS

<b>Title:</b>	Randomized controlled trial of mindfulness-based stress reduction plus prenatal sleep supplement versus usual care: Acceptability, feasibility, and adherence
<b>Grant Number:</b>	K23AT009896
<b>Study Description:</b>	The goal of this trial is to conduct a pilot randomized controlled trial to evaluate mindfulness-based stress reduction plus prenatal sleep supplement to improve prenatal sleep (MBSR + PS) compared to treatment as usual (TAU). Our primary focus is on evaluating acceptability, feasibility, and adherence. Secondly, we will explore condition differences in hypothesized targets (i.e., psychological responses to nightly physical symptoms) and the clinical outcome of interest (i.e., subjective sleep quality).
<b>Objectives:</b>	Primary Objectives: Acceptability, feasibility, adherence Secondary Objectives: Change in psychological responses to nightly physical symptoms; between group differences in global sleep quality
<b>Endpoints:</b>	Primary Endpoint: Willingness to be randomized, treatment initiation, reasons for attrition, satisfaction; Yield of eligible participants, number randomized, retention rate, completeness, missingness; Session attendance, home practice completion Secondary Endpoints: 14-day daily diary, validated retrospective measures of psychological constructs hypothesized as mediators; subjective sleep quality
<b>Study Population:</b>	50 women 12-28 weeks gestation with poor sleep quality
<b>Phase:</b>	Stage 1B in the NIH Stage Model for behavioral intervention development
<b>Description of Site Enrolling Participants:</b>	Single site study at University of California, San Francisco.
<b>Description of Study Intervention:</b>	The study intervention is standard mindfulness-based stress reduction (MBSR). The supplemental prenatal sleep content draws material from mindfulness-based therapy for insomnia, mindfulness-based childbirth and parenting program, and cognitive behavior therapy for prenatal insomnia.
<b>Study Duration:</b>	12 months
<b>Participant Duration:</b>	Approximately 3 months

## 1.2 SCHEMA

### Flow Diagram



### 1.3 SCHEDULE OF ACTIVITIES

<b>Timepoint</b>	<b>Screening</b>	<b>Baseline</b>	<b>Daily</b>	<b>Weekly</b>	<b>Endpoint</b>
<b>Allowable window</b>	<b>N/A</b>	<b>0-4 weeks prior to randomization</b>	<b>Within 24 hours</b>	<b>Within 3 days</b>	<b>+/- 4 weeks</b>
Screening consent	x				
Screening measures	x				
Demographic form	x				
Orientation session	x				
Study consent	x				
14-day daily diary		x			x
Outcome measures		x			x
Depression measure				x	
Home practice measure (MBSR+PS only)			x		
Sleep diary (MBSR+PS only)			x		
Use of non-study treatments questionnaire		x			x
Adverse events questionnaire					x
Client Satisfaction Questionnaire					x

## 2 INTRODUCTION

### 2.1 STUDY RATIONALE

Poor sleep quality is highly prevalent during pregnancy,<sup>1</sup> with important implications for maternal and infant health and well-being. That is, poor sleep is associated with increased risk of: depression;<sup>2,3</sup> suicidal ideation;<sup>4</sup> gestational diabetes;<sup>5</sup> preterm birth;<sup>6,7</sup> and caesarean birth.<sup>8,9</sup> Despite this, there is limited research on interventions to improve prenatal sleep, and prior research did not target the specific factors contributing to poor sleep quality in this population.

Specifically, pregnant women report that physical symptoms, including discomfort and pain, disturb their sleep.<sup>1</sup> In non-pregnant populations, the pain-sleep relationship is bidirectional,<sup>10</sup> and maladaptive psychological responses to pain further exacerbate poor sleep.<sup>11,12</sup> Although pregnancy-related discomfort and pain may be difficult to eliminate, psychological responses to such symptoms offer modifiable targets to break the pernicious discomfort/pain – poor sleep cycle.

Theory and empirical evidence indicate that mindfulness-based interventions may be effective for targeting these psychological responses. For example, mindfulness-based stress reduction (MBSR) teaches skills to accept difficult, unchangeable experiences (like chronic pain<sup>13</sup>), and randomized controlled trials demonstrate improvements in sleep<sup>14</sup> and responses to pain<sup>15-17</sup> in non-pregnant populations. MBSR has been adapted to teach skills for coping with intense sensations during pregnancy and birth (mindfulness-based childbirth and parenting, MBCP)<sup>18</sup> and to improve sleep among individuals with chronic insomnia (mindfulness-based therapy for insomnia, MBTI).<sup>14,19</sup> However, there is a paucity of research optimizing and evaluating mindfulness-based interventions for improving prenatal sleep quality.

The goal of this trial is to conduct a pilot randomized controlled trial to compare a program consisting of MBSR plus prenatal sleep content (MBSR+PS) to treatment as usual (TAU). Our primary focus is on evaluating acceptability, feasibility, and adherence. Secondly, we will explore condition differences in hypothesized targets (i.e., psychological responses to nightly physical symptoms) and the clinical outcome of interest (i.e., subjective sleep quality).

### 2.2 BACKGROUND

Poor sleep quality during pregnancy is common and associated with negative correlates and consequences for mom and baby. Over 75% of pregnant women report poor sleep quality, which is linked to adverse psychological and obstetric outcomes, such as increased risk of depression symptom severity,<sup>20</sup> suicidal ideation after accounting for depression,<sup>4</sup> gestational diabetes mellitus,<sup>5</sup> preterm birth,<sup>6-8</sup> and caesarean birth.<sup>8,9</sup> Moreover, prenatal poor sleep quality often persists into the postpartum period,<sup>20</sup> thereby maintaining and exacerbating postpartum depression.<sup>21</sup> Thus, improving poor sleep quality during pregnancy may have significant health implications for both mother and offspring.

Pregnant women report that pregnancy-related physical symptoms, including discomfort, back pain, and hip/pelvic pain, disturb their sleep.<sup>1</sup> Longitudinally, such symptoms predict worsening sleep quality.<sup>22</sup> In non-pregnant populations, the pain-poor sleep association is bidirectional,<sup>10</sup> and poor sleep exacerbates discomfort and pain.<sup>23,24</sup> It may be challenging to eliminate pregnancy-related discomfort and pain, but psychological responses are modifiable targets to break the pain/discomfort-poor sleep cycle. In studies of individuals with chronic pain, acceptance of pain predicted lower insomnia severity, after accounting for pain severity,<sup>11</sup> and presleep rumination about pain was associated with longer sleep latency, after accounting for pain severity.<sup>12</sup> Our preliminary data in a sample of 50 pregnant women indicated that physical symptoms were the most common reason women had trouble falling or staying asleep, relative to difficulties quieting the mind, other, or unknown. The psychological responses that had the strongest associations with sleep quality were: “I felt annoyed or bothered by my physical symptoms” ( $r = -0.29$ ), “I reassured myself that my symptoms were normal” ( $r = 0.17$ ), and “I paid attention to my physical symptoms without trying to change them” ( $r = 0.16$ ).

Current options for improving prenatal sleep are limited, but pregnant women want help. There is limited research on acceptable and effective interventions to improve sleep during pregnancy. Prescription medications, such as zolpidem, may be associated with increased risk of adverse birth outcomes<sup>25</sup> and pregnant women prefer non-pharmacological interventions for sleep.<sup>26</sup> The small body of research examining non-pharmacological interventions for improving sleep during pregnancy have used cognitive behavioral approaches to treat chronic insomnia. Such approaches target dysfunctional sleep beliefs and behaviors, but do not target the unique factors contributing to poor sleep quality during pregnancy. Previously, we found that significantly more pregnant women with insomnia who were randomized to digital cognitive behavior therapy for insomnia experienced remission in insomnia symptoms relative to women randomized to standard care;<sup>27</sup> however, most women continued to experience at least subthreshold symptoms. Thus, targeting pregnancy-specific sleep disturbances, such as nocturia and discomfort, may help more women achieve symptom remission. Mindfulness-based and acceptance-based approaches that focus on increasing acceptance of physical symptoms that may be difficult to eliminate may be particularly well suited for pregnancy-related poor sleep. Taken together, these data emphasize the need for alternative approaches to improving prenatal poor sleep quality by addressing key mechanisms.

Mindfulness-based intervention may be a promising approach for improving pregnancy-related factors of poor sleep quality. Mindfulness-based stress reduction (MBSR) was developed to reduce psychological reactivity to chronic pain.<sup>28</sup> In a group intervention, MBSR participants learn skills to notice and accept difficult, often unchangeable, sensations, emotions, and thoughts. Randomized clinical trials of MBSR among non-pregnant populations demonstrate significant effects on the psychological mechanisms (pain acceptance<sup>15,16</sup> and rumination<sup>17</sup>) that we hypothesize contribute to poor sleep quality during pregnancy, as well as on objective and subjective measures of sleep,<sup>14</sup> even in the context of chronic pain.<sup>29</sup> Additionally, mindfulness-based therapy for

insomnia (MBTI) is effective for improving sleep among individuals with chronic insomnia.

Nearly a quarter of pregnant women report using mind-body practices,<sup>30</sup> and more pregnant women prefer mind-body intervention to pharmacotherapy for improving sleep.<sup>26</sup> However, there is a paucity of research optimizing and evaluating a mindfulness-based intervention for improving sleep during pregnancy. The current trial seeks to address this critical gap. Improving sleep quality during pregnancy has the potential to avert its myriad negative consequences, with considerable implications for women and their families.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

**MBSR+PS:** Participation in the study intervention carries minimal risk of emotional discomfort. It is possible that participants may experience injury or discomfort during mindful stretching and walking practice; however, such practices may also improve pain during pregnancy.<sup>31</sup> Previous studies of mindfulness-based interventions, including in pregnant populations, demonstrate safety and acceptability, with no adverse events reported. Some participants may be advised to implement techniques designed to consolidate sleep. These techniques reduce the amount of time spent awake in bed, which increases sleep drive, and ultimately decreases sleep onset latency and wake after sleep onset. Participants may experience temporary increases in sleepiness during this component of treatment. Two previous trials that included this technique among pregnant women found no unanticipated serious adverse events.<sup>27,32</sup> We are aware of no research to suggest that the proposed intervention would confer risk to fetal, obstetric, or infant outcomes. At this time, there is a paucity of other treatments specifically for pregnancy-related poor sleep quality. Pharmacotherapy is associated with adverse birth outcomes,<sup>25</sup> and pregnant women prefer non-pharmacological treatments.<sup>26</sup> Cognitive behavior therapy targets maladaptive sleep beliefs and behaviors that are unique to chronic insomnia, and it does not address pregnancy-related factors of poor sleep quality.

**Self-report questionnaires:** There are no known risks for completing the study questionnaires, though it is possible that participants may experience temporary discomfort from thinking about their physical symptoms, psychological responses, and sleep.

**Actigraphy (optional depending on COVID-19 guidelines; see Section 8.1):** There is no risk of injury from the wrist-actigraph to measure sleep, though it may feel like a slight inconvenience wearing a wrist device for 14 days. There may be a risk of allergy to the metal of the actigraph device.

**Confidentiality of data:** Although every reasonable effort will be taken, confidentiality on web-based surveys cannot be guaranteed. It is possible that information may be captured and used by others who are not associated with this study.

**Inconvenience:** There may be some burden associated with completing the questionnaires and attending intervention sessions.

**Worsening depressive symptoms and/or suicidal ideation:** As is true for non-perinatal individuals generally, participants with poor sleep quality may experience increases in depressive symptoms and/or suicidal ideation, independent from their involvement in the study.

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### 2.3.2 KNOWN POTENTIAL BENEFITS

Previous research suggests that mindfulness-based interventions are associated with improvements in sleep<sup>14</sup> and responses to pain<sup>15-17</sup> in non-pregnant populations. All participants may benefit from ongoing monitoring of and referral for depression incidence or suicidality. In the long-term, there are substantial benefits to be gained by optimizing a mindfulness-based intervention to improve prenatal sleep.

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### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

**MBSR+PS** Participants will be provided with a thorough description of the intervention prior to randomization, and notified that they can withdraw participation at any time without penalty. Given the physical and psychological consequences of poor sleep quality during pregnancy, we expect that the proposed intervention would be associated with improved outcomes. However, important precautions will be taken to minimize physical risks. Participants will be provided the American College of Obstetrics and Gynecology list of indicators to terminate exercise. Participants will be advised to stop the physical activity if these signs are present, and to contact their obstetric health care provider. We will ask participants to alert us if they experience an increase in daytime sleepiness, and will advise them about the risks of driving or doing any activity where severe sleepiness puts them at danger, and will instruct them to take naps if they feel sleepy.

**Self-report questionnaires:** Participants will be allowed to skip any questions they do not feel comfortable answering. One exception is that participants will be informed during the initial screening that skipping questions that are necessary for determining eligibility may preclude their ability to participate in the study. Additionally, because all questionnaires will be completed online, participants can complete them in a location and at a pace that feels comfortable to them.

**Actigraphy (optional depending on COVID-19 guidelines; see Section 8.1):** In case of allergy, participants can wear the monitor over their sleeve or use a wrist sports sweatband to protect their skin.

**Confidentiality:** All data will be handled with the utmost attention to participants' confidentiality. Participants will be assigned unique, coded, confidential identifiers that will be used to label all data forms, data entries, and questionnaires. The key linking the participants' identity to their unique coded identifier will be stored on a cloud-based collaboration tool that uses access controls and encryption, and is safe for storing protected health information. Access to all data will be limited to the PI and trained,

authorized study staff.

One limit to confidentiality is if a participant indicates she is at imminent risk of harming herself. If a participant endorses PHQ-9 item 9, a pop-up will immediately appear with instructions to call 911 or go to the nearest emergency room for a life-threatening emergency. Additionally, email triggers will immediately notify study staff, who will call to conduct a risk assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS). At the beginning of the C-SSRS assessment, study staff will ask the participant for her current location. Study staff will provide psychological referrals for low to medium risk. For immediate risk, the study staff will direct the participant to the nearest emergency room and/or to call 911. If the participant declines, the study staff will call the participant's local emergency services number, which will be recorded in the participant tracking database at enrollment. Study staff will immediately notify Co-Investigator Dr. Krystal, a psychiatrist with experience working with depressed and suicidal individuals, anytime a participant endorses suicidality. He will provide further supervision as deemed necessary and will determine whether additional follow-up assessment is indicated. Principal Investigator Dr. Felder, a licensed clinical psychologist with experience working with depressed perinatal women, will be a back-up if Dr. Krystal is unavailable.

**Worsening depressive symptoms:** Participants will be instructed to make immediate contact with study personnel with any questions or concerns regarding worsening depression symptoms. At enrollment, we will provide contact information for Dr. Krystal, Dr. Felder, therapeutic resources, and crisis hotlines. We will closely monitor depressive symptom severity via weekly administration of the PHQ-9. Study staff will recommend that any participant who scores above the PHQ-9 cutoff ( $\geq 10$ ) notify her obstetrician. Additionally, study staff will recommend that participants who score above the cutoff seek treatment for depression and will provide local resources using the Postpartum Support International "Find Local Support and Help" resource (<https://www.postpartum.net/get-help/locations/>).

**Inconvenience:** Every effort will be taken to reduce participant burden, and participants will be compensated for their time and effort.

### 3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	METRIC
Primary			
To determine acceptability	<ol style="list-style-type: none"> <li>1. Willingness to be randomized</li> <li>2. Treatment initiation</li> <li>3. Reasons for attrition</li> <li>4. Satisfaction</li> </ol>	One of the primary study objectives of this pilot RCT is to determine the acceptability of the MBSR+PS intervention and the study procedures.	<ol style="list-style-type: none"> <li>1. Among women determined to be eligible to participate, we aim for <math>\geq 80\%</math> to indicate willingness to be randomized</li> <li>2. We aim for <math>\geq 85\%</math> MBSR+PS participants to attend at least one session of MBSR and the PS supplement</li> <li>3. Assessed qualitatively</li> <li>4. Among participants randomized to MBSR+PS, we aim for a total score <math>\geq 24</math> on the Client Satisfaction Questionnaire</li> </ol>
To determine feasibility	<ol style="list-style-type: none"> <li>1. Yield of eligible participants</li> <li>2. Number randomized</li> <li>3. Retention rate</li> </ol>	One of the primary study objectives of this pilot RCT is to determine the feasibility of the MBSR+PS intervention and	<ol style="list-style-type: none"> <li>1. Defined as # Eligible / # Assessed for Eligibility</li> <li>2. N=50 within study timeline</li> </ol>

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	METRIC
	4. Completeness 5. Missingness	the study procedures.	3. Our goal is for $\geq 80\%$ of randomized participants to complete endpoint measures  4. For a measure to be considered complete, at least 95% of items must be completed. We aim for $\geq 95\%$ of participants who are participating at a particular time point to complete each scale  5. Explore patterns of incomplete data and investigate possible missingness mechanisms (i.e., missing completely at random, missing at random, missing not at random).
To determine adherence	1. Session attendance 2. Home practice completion	One of the primary study objectives of this pilot RCT is to determine participant	1. We aim for an average of at least 50% of MBSR and PS supplement

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	METRIC
		adherence to the MBSR+PS intervention.	<p>sessions attended.</p> <p>2. We will examine the frequency and duration of formal and informal practices</p>
Secondary/Exploratory			
To explore evidence of change in psychological mediators	<ol style="list-style-type: none"> <li>14-day daily diary</li> <li>Validated retrospective measures of psychological constructs hypothesized as mediators</li> </ol>	A secondary study objective is to explore group differences in change on potential mechanistic outcomes.	Non-acceptance, avoidance, self-compassion, rumination, worry, mindfulness, as measured by 14-day daily diary and validated retrospective measures (Self-Compassion Scale-Short Form; Rumination-Reflection Questionnaire; Five Facet Mindfulness Questionnaire; Coping Strategy Scale)
To explore between-group differences in sleep	Subjective sleep	A secondary objective is to explore change in clinical outcome. In future research, we expect that our primary clinical endpoint will be global sleep quality.	Pittsburgh Sleep Quality Index scores (primary); Insomnia Severity Index; Dysfunctional Beliefs About Sleep; Measures for coping with sleep disturbances;

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	METRIC
			Worry about sleep (secondary)
To explore group differences in other critical clinical outcomes	<ol style="list-style-type: none"> <li>1. Depressive symptoms</li> <li>2. Anxiety symptoms</li> <li>3. Stress</li> </ol>	A secondary objective is to explore change in mental health clinical outcomes.	<ol style="list-style-type: none"> <li>1. PHQ-9</li> <li>2. PROMIS 6-item anxiety measures</li> <li>3. Perceived Stress Scale</li> </ol>

## 4 STUDY DESIGN

### 4.1 OVERALL DESIGN

**Hypotheses:** The primary goal of this pilot RCT is to test acceptability, feasibility, and adherence using the metrics described above. Secondly, we will explore evidence of change in primary mechanistic outcomes (e.g., psychological responses to nightly physical symptoms), and group differences in our primary clinical outcome (i.e., sleep quality).

**Trial phase:** This feasibility trial is considered trial Stage 1B in the NIH Stage Model for Behavioral Intervention Development.

**Trial design:** This is a single-site, randomized controlled trial comparing MBSR+PS to TAU.

**Randomization (see also section 6.3):** Participants will be randomized to MBSR+PS or TAU after the baseline assessment. Randomization will be blocked to reduce imbalance in condition assignment and conducted by an independent investigator. Consistent with standard procedures, the independent investigator may use multiple block lengths but will not tell study staff the number or length of blocks. Participants will be notified of their assignment by phone and email.

We considered stratifying randomization by gestational age but decided against it for the following reasons: 1) we are enrolling participants in a fairly narrow gestational age range (12-28 weeks gestation), reducing the need for stratification; 2) using stratification in a blocked randomization scheme may make it too easy to anticipate future allocations; 3) the need for stratification is low considering we have the computing power to adjust for unbalanced covariates if needed; and 4) there may be significant

practical challenges meeting enrollment and timeline targets with both a narrow gestational age range and stratification. We will implement stratified randomization in future research if data from this feasibility trial indicate it is necessary.

**Study interventions:** Participants are randomized to one of two conditions: MBSR+PS + TAU or TAU alone.

For TAU, participants are permitted to receive standard care for prenatal sleep disturbance. That is, there are no constraints on treatment, including medication or psychotherapy, with the exception of asking participants to refrain from participating in non-study mindfulness practice.

Additionally, MBSR+PS participants will receive standard MBSR plus supplemental prenatal sleep content. The MBSR groups will be offered via Zoom through publicly-available, existing MBSR program courses that are linked to an academic medical center or hospital. Participants will be randomized to MBSR programs at the UCSF Osher Center for Integrative Medicine, Brown University Mindfulness Center, or the UCSD Center for Mindfulness. If needed to meet enrollment targets, participants may also be randomized to MBSR programs taught at the UMass Memorial Health Center for Mindfulness and Bob Stahl's ART Mindfulness Program. Participants will only be randomized to MBSR courses for which the instructor confirms that there are no substantial modifications to the standard curriculum. All MBSR groups will be comprised of heterogeneous groups, including non-pregnant people.

The prenatal sleep content:

- Draws material from the mindfulness-based therapy for insomnia program, the research on cognitive behavior therapy that specialized advisor Dr. Rachel Manber and I have done with pregnant women with insomnia, and the mindfulness-based childbirth and parenting program.
- Will be delivered via Zoom in brief ( $\leq 30$  minutes) weekly sessions designed to supplement the MBSR course by an instructor with behavioral sleep medicine training.
- Can be delivered to small groups of pregnant women or one-on-one.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We selected TAU as the comparator group because our goals are to document clinically significant signal above and beyond usual care and to maximize between-group differences in the primary mechanistic outcomes<sup>33</sup> at this early stage of research. Further, TAU is a clinically relevant comparator by nature. We opted against a no treatment comparator due to ethical concerns about withholding treatments that the population may need and otherwise receive.

## 4.3 JUSTIFICATION FOR INTERVENTION

We will deliver MBSR+PS via video conferencing (i.e., Zoom platform) instead of via in-person sessions for several reasons. First, delivering the intervention remotely affords

us more flexibility and the ability to continue study activities even in the context of potential COVID-19 shelter-in-place orders. Second, pregnant women may have a lower tolerance for risk for attending in-person visits when there are spikes in COVID-19 activity. Third, we want to develop a program that has high potential for scalability and ultimately plan to deliver the intervention remotely in efficacy testing. Thus, the feedback we will get in this feasibility trial will be more relevant. Finally, delivering the intervention remotely is responsive to focus group feedback that women do not want an all in-person intervention.

MBSR will be offered in its typical session format: in 8 weekly sessions with an all-day retreat. The prenatal sleep content will be offered in 6-8 weekly brief sessions designed to be 30 minutes or less. Data will be analyzed on an intent-to-treat basis, and we aim for an average percentage of sessions attended  $\geq 50\%$ .

#### 4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study once she has completed the endpoint measures. The end of the study is defined as the final participant's completion of the endpoint measures shown in the Schedule of Activities (SoA), **Section 1.3**.

### 5 STUDY POPULATION

#### 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Currently pregnant 8-28 weeks gestation. This ensures that participants can learn strategies to improve their sleep before the end of the third trimester when sleep quality is the poorest, and can complete the intervention prior to birth.
2. 18 years or older. Adolescents have unique sleep needs that are not addressed in the proposed intervention.
3. Daily access to a web-enabled computer, phone, or tablet. Access is necessary to participate in the weekly interventions sessions, which are delivered via Zoom, and for the 14-day daily online sleep diaries, in which participants receive an automated email or text message with a personalized survey link to complete upon awakening each morning.
4. Ability to read and speak English, and to provide informed consent. The intervention will be delivered in English, and we do not have the capacity, given the resources available in this project, to translate all course material and conduct groups in another language.
5. Poor sleep quality (PSQI  $> 5$ ). The ultimate goal of the proposed research is to improve poor sleep quality.

## 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Self-reported sleep disorder not likely to improve with MBSR+PS (e.g., sleep apnea, narcolepsy, parasomnia, circadian rhythm disorder).
2. Shift-work or nighttime caregiving responsibilities. Irregular sleep/wake patterns would make it difficult to evaluate the impact of the intervention.
3. Psychological, medical, or other issues that necessitate priority treatment or that would preclude participation (e.g., active suicidality, probable depression, psychosis, on bed rest, multiple gestation).
4. Current regular mindfulness practice (>20 minutes/week). Regular mindfulness practice aside from the study intervention would risk contamination of study outcomes.

## 5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to refrain from participating in non-study mindfulness practices. At endpoint, we will measure participation in non-study mindfulness practices. We view this as informative data to gather in this feasibility trial, and will not withdraw participants for participating in non-study mindfulness practices.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. An example includes the lifting of bed rest restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

**Anticipated number to be screened:** We conservatively estimate that we may need to screen approximately 550 women to reach the target enrollment size of 50. This estimate is based on our previous trial evaluating digital cognitive behavioral therapy for prenatal insomnia, which used more stringent eligibility criteria.

**Sample size and demographics:** We will randomize 50 participants with the goal of obtaining endpoint data from 40 (50 randomized x 80% anticipated retention = 40 with endpoint data). The purpose of the proposed research is to optimize MBSR+PS to improve poor sleep quality among pregnant women. Therefore, all participants will be women. There are no 12 or exclusion criteria based on race or ethnicity. Minority

inclusion will be representative of the San Francisco Bay Area 2010 Census results. We expect that approximately 50% of participants will be White, and approximately 15% will be Hispanic or Latina.

**Recruitment sources:** We will primarily recruit participants from two sources: 1) UCSF Obstetrics and Gynecology clinics via electronic health record, direct mail, and electronic flyers in waiting rooms (anticipated n = 25), and 2) Facebook advertisements (anticipated n = 25). We have successfully employed these methods in previous clinical trials with pregnant women at UCSF.

If needed, we will recruit participants via listservs, social media groups and accounts, and publications that serve a pregnant audience, and post ads in community, medical, and retail settings (e.g., grocery stores, maternity clothing stores, toy stores).

We will ensure a diverse, representative sample by using advertisement images featuring racially and ethnically diverse pregnant women and by using targeted recruitment text (e.g., “Recruiting pregnant Latina women”). If needed, we will utilize Facebook’s audience selection tool to display our ads in zip codes that have a higher proportion of racially and ethnically diverse populations.

**Procedure for identifying participants:** For women recruited through UCSF Obstetrics and Gynecology clinics, MyChart (Apex) conducts a search for patients based on the study’s inclusion and exclusion criteria. This is a completely computer-aided search, meaning the computer – not a person – searches patient charts. When a patient is identified as potentially eligible, they receive an email from MyChart that says to log in to MyChart to read about a study they might be interested in. The email is short and is the same for every recipient—there is no patient-specific, study-specific or disease information in it. When the patient logs into MyChart, there is a new “Research” tab with template information about participating in research and how to opt out of receiving recruitment messages. Then, the patient can click through to learn about a specific study they may be eligible for. The patient has the option of clicking a link/button to let the study team know that they are interested in learning more about the study. Only if the patient takes this action will the study team receive information about the patient. If the patient clicks “No thanks” or simply does not respond, they will not be contacted by the study team, they won’t receive any follow-up emails from MyChart about this study, and their information will not be shared with the study team. To address racial and ethnic disparities that exist in MyChart enrollment, we will also collaborate with the CTSI Participant Recruitment Program (PRP) to send paper letters to patients who are not enrolled in MyChart. CTSI PRP will act as an honest broker of the EHR data and sends letters to the cohort directly, ensuring privacy and confidentiality of patients identified. The data extract will be done using APeX reports and will be downloaded and stored in the CTSI PRP MyResearch account. The CTSI PRP will coordinate the mailing on behalf of the study and will send the Dear Patient letter to UCSF patients identified in these reports. Interested subjects will contact the study staff as described in the letter. Protected data elements included in the data pull may include MRN, name, mailing address, and diagnosis or encounter date.

Women who view our IRB-approved ads on Facebook will be directed to complete the online eligibility survey or to contact study staff directly to learn more about the study.

**Accrual rate:** We will begin randomizing women in September 2021 to complete data collection by August 2022.

**Justification for inclusion of vulnerable participants:** The rationale for our focus on the vulnerable population of pregnant women is informed by the exceedingly high prevalence of poor sleep quality during this critical lifecycle phase, the consequences of prenatal poor sleep quality, and the limitations of existing interventions.

**Retention strategies:** We will utilize the following methods to encourage measure completion, which have been successful in our previous clinical trials with pregnant women:

1. Conduct an orientation session prior to randomization, which is shown to increase adherence and retention. Participants will learn about: the scientific importance of the trial; what participation entails; rationale for the control condition and random assignment; and the effect of attrition bias. Participants will be asked to generate two pros and two cons of participating in the study and not participating in the study, and to carefully consider whether or not to participate.
2. Create a project identity that participants can recognize using a study logo, and similar colors and fonts on trial materials.
3. Write protocols to address common participant questions.
4. Embody a “gracious and tenacious” approach by making multiple, standardized attempts to contact participants via phone, email, and text message to complete measures.
5. Send birthday cards to maintain connection with participants.
6. Request contact information for someone we have permission to contact if we lose touch with participant.
7. Provide monetary incentives for completing measures:
  - a. \$25 upon completion of baseline self-report measures
  - b. Up to \$100 for baseline daily diaries (depending on number of diaries completed)\*
  - c. \$25 upon completion of endpoint self-report measures
  - d. Up to \$100 for endpoint daily diaries (depending on number of diaries completed)\*

\*If participant is wearing wrist actigraph (optional depending on local COVID-19 guidelines; see Section 8.1), then compensation will be sent upon study team's receipt of actigraph.

## 6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

### 6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

#### 6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Participants will be randomly assigned to either the intervention condition, mindfulness-based stress reduction plus prenatal sleep supplement (MBSR+PS) or the control condition, treatment as usual (TAU).

The MBSR+PS program involves standard MBSR plus supplementary prenatal sleep content. The prenatal sleep content includes psychoeducation about sleep during pregnancy, applies mindfulness principles to sleep, and teaches behavioral principles for improving sleep. In our preliminary work, pregnant women described maladaptive behavioral responses that may perpetuate sleep problems, such as lying in bed for hours looking at their phone. Thus, the intervention also draws from cognitive behavior therapy for insomnia (CBT-I) and the mindfulness-based therapy for insomnia (MBTI) program to integrate behavioral recommendations for improving sleep with mindfulness techniques (e.g., stimulus control).

All participants will be asked to refrain from participating in non-study mindfulness programs to prevent contamination. There are no other constraints on treatment, including medication or psychotherapy (treatment as usual; TAU). If a participant develops a sleep disorder (e.g., sleep apnea) over the course of the study, we will provide a list of referrals for further evaluation and treatment; such participants will be allowed to remain in the study.

#### 6.1.2 ADMINISTRATION AND/OR DOSING

The full-dose MBSR+PS program will consist of:

Standard MBSR:

- 8 weekly sessions
- All day retreat
- Administered by a trained and vetted MBSR instructor via Zoom
- Delivered to heterogenous groups, including non-pregnant women

Prenatal Sleep Content:

- 6-8 weekly brief sessions ( $\leq 30$  minutes) via Zoom
- Flexibly designed to be delivered 1:1 or to small groups of pregnant women

- Delivered by an instructor with behavioral sleep medicine training

## 6.2 FIDELITY

### 6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Prior to randomizing participants to a particular MBSR class, we will request that the class instructor complete a brief survey with the following items:

1. In the MBSR classes you teach, do you make any substantial modifications to the standard curriculum? If yes, please describe. (We will not randomize participants to MBSR classes with substantial modifications to the standard curriculum)
2. How many years of experience do you have teaching MBSR? (This descriptive data will be reported in publications; We will not exclude MBSR classes based on instructor responses to this item.)
3. Over the past 3 years, how many total days have you spent at mindfulness retreats? (This descriptive data will be reported in publications; We will not exclude MBSR classes based on instructor responses to this item.)

All prenatal sleep content sessions will be recorded on the Zoom platform. Dr. Felder will review 10% of audio-recorded sessions to ensure that the key elements of the curriculum content are addressed.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will be blocked to reduce imbalance in condition assignment and conducted by an independent investigator. Consistent with standard procedures, the independent investigator may use multiple block lengths but will not tell study staff the number or length of blocks. Participants will be notified of their assignment by phone and email.

We have carefully considered the issue of blinding, and have decided the following:

- **Principal investigator:** Blinded to condition assignment.
- **Randomizer:** Unblinded by necessity but will be independent from the study and have no access to the data and/or influence on outcome assessments.
- **Project coordinator and research assistants:** Unblinded to condition assignment in order to permit day-to-day management of the trial, including notifying participants of randomization, assisting the clinician with intervention delivery, and responding to participant questions. Although these staff members will assist with data collection, all measures are self-report via online surveys. No measures are interviews or clinician-rated, thus mitigating concerns about the effect of unblinding on outcome assessment.

- **Data manager:** Blinded to condition assignment.
- **Participants and clinicians:** Unblinded to condition assignment by necessity because we are comparing MBSR+PS to treatment as usual.

We do not anticipate any situations that would require breaking the study blind. Drs. Krystal and Hecht are unblinded and able to respond to safety concerns and serious adverse events.

## 6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

As in our previous research, we will use a REDCap database to track and retain participants for follow-up assessments. The tracking file will contain each participant's current status in the study (e.g., enrolled, completed); dates when consent documents are completed, when measures are due, and when measures are completed; and an open text field for comments.

Adherence is operationalized as session attendance and home practice completion. We will enter weekly MBSR+PS attendance into the REDCap database. Participants will be asked to complete a brief daily survey of home practice completion, and home practice completion will be recorded into the REDCap database. Finally, we will track whether participants access and download intervention materials.

To permit intention-to-treat analyses, we will follow participants even if they cease to adhere to the protocol, regardless of condition assignment.

## 6.5 CONCOMITANT THERAPY

At endpoint, we will assess the type, frequency, and duration of non-study treatments, including the use of pharmacotherapy, psychotherapy, natural remedies, and psychiatric hospitalization.

### 6.5.1 RESCUE THERAPY

N/A

## 7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

We do not anticipate any reasons for the investigators to discontinue the study intervention for participants. Participants can decide to discontinue the study intervention and to continue participating in the study by completing follow-up

measures. Participants who become ineligible (e.g., no longer pregnant due to miscarriage) will have the option to continue both the intervention and the study.

If a participant discontinues the intervention, we will record their reason(s) for discontinuing the intervention.

If the participant is due to complete assessments within 2 weeks of discontinuing the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. We do not anticipate that the investigators will discontinue any participant from the study.

## 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up at a particular timepoint if she fails to respond within the allowable response window (See table in Section 1.3). The following actions will be taken to minimize loss to follow-up:

- Study staff will contact participants via a range of methods (email, phone, text, letter) at least 3 times to remind them to complete study measures within the allowable response window. These contact attempts will be documented in the participant tracking database.
- If the above attempts are unsuccessful, study staff will contact the participant's secondary contact person to find out the best method of reaching the participant and/or to have the secondary contact person ask the study participant to contact study staff.
- Should the participant continue to be unreachable at a particular timepoint, study staff will continue to send follow-up assessments at each subsequent timepoint. Participants will not be withdrawn due to lost to follow-up at any timepoint.

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

See the Table in Section 1.3 for an overview of timepoints, allowable response windows, and measurement schedule.

**Screening timepoint:** Participant demographic data will be collected to determine eligibility (e.g., age) and to fully characterize the sample (e.g., race, ethnicity, highest

level of education attained, income, marital status, number of children and their ages, zip code, insurance type, employment status). Eligibility criteria will be assessed using a screening survey that assesses:

- self-report of pregnancy status and gestational age in weeks
- confirmation of pregnancy via an ultrasound image, after visit summary, appointment reminder, bill, or similar document that includes participant name and date. Women can choose to upload this documentation into the eligibility survey, display the documentation during the orientation visit, or send the document via secure email.
- self-reported daily access to a web-enabled computer, phone, or tablet self-reported ability to read and speak English
- self-reported diagnosis of sleep apnea, narcolepsy, parasomnia, or circadian rhythm disorder
- validated Facco algorithm to screen for sleep apnea during pregnancy
- validated Morning-Eveningness Questionnaire to screen for circadian rhythm disorder
- self-reported experience of sleepwalking, sleeptalking, nightmares to assess for parasomnia
- self-reported night shift work in the past month or next month
- self-reported nighttime caregiving responsibilities
- validated Patient Health Questionnaire-9 to assess for depression and/or suicidality
- self-reported diagnosis of schizophrenia or bipolar disorder
- self-reported on bed rest
- self-reported pregnancy with multiples

**Baseline timepoint:** Participants will complete two types of assessments at the baseline timepoint: 14 daily sleep diaries and outcome measures.

**14 day online daily sleep diaries:** To assess the mechanisms of pregnancy-related physical symptoms-poor sleep association, we will use daily diary methods to capture data on the dynamic, longitudinal associations between nightly physical symptoms, psychological responses (i.e., acceptance, self-compassion, rumination, worry, mindfulness, maladaptive pain coping), and sleep quality. Each morning for 14 consecutive days, participants will complete a diary assessing:

- Last night's sleep using the validated consensus sleep diary
- Disruptors of sleep (physical symptoms, anxiety/worry, mind racing)
- Psychological responses to nightly physical symptoms

Depending on local COVID-19 guidelines, we may also use wrist-actigraphy to assess our secondary clinical outcome, objective sleep behaviors (total sleep time, sleep latency, wake after sleep onset, number of awakenings, sleep efficiency). We will collect these data only if local guidelines permit research as usual. Sending and receiving the wrist actigraphs requires multiple trips per week to FedEx, and we do not want to risk staff safety to collect this secondary outcome. Further, we have adequate feasibility data collecting actigraphy data from 50 pregnant women in our preliminary research (Aim 1 of K23).

**Outcome measures:** Consistent with our preliminary research (Aim 1 of K23), we will collect data on nightly physical symptoms, psychological mediators, and sleep quality using retrospective, self-report measures. We received feedback from Aim 1 participants that completing these online measures was not burdensome, and we had no missing data.

- Pregnancy Symptoms Inventory previously adapted to measure nightly sleep disturbances
- Measures of psychological mediators:
  - Self-Compassion Scale - Short Form
  - Rumination-Reflection Questionnaire
  - Five Facet Mindfulness Questionnaire
  - Coping Strategy Scale
- Measures of sleep:
  - Pittsburgh Sleep Quality Index
  - Insomnia Severity Index
  - Dysfunctional Beliefs About Sleep
  - Measures for coping with sleep disturbances
  - Worry about sleep
- Other clinical outcomes:
  - Patient Health Questionnaire-9

- PROMIS 6-item anxiety measure
- Perceived Stress Scale
- Contemplative practices and stress management techniques

**Daily measures:** Participants randomized to MBSR+PS will be asked to complete a brief daily home practice measure and the consensus sleep diary from the first until the last intervention session.

**Weekly measures:** Participants will complete a depression measure (Patient Health Questionnaire-9) once per week from randomization until endpoint.

**Endpoint measures:** Participants will complete the same outcome measures as at the baseline timepoint, as well as the Client Satisfaction Questionnaire and adverse events questionnaire.

## 8.2 SAFETY ASSESSMENTS

We plan to use the Patient Health Questionnaire-9 to monitor depressive symptom severity. PHQ-9 scores range from 0-27, with scores  $\geq 10$  indicating moderate-to-severe depression. Item 9 assesses “thoughts that you would be better off dead, or of hurting yourself in some way.” At screening, women with PHQ-9  $\geq 10$  or who endorse item 9 will be excluded from participation. Among enrolled participants, we will closely monitor depressive symptom severity and suicidal ideation via weekly administration of the PHQ-9. Qualified study personnel will make appropriate referral for community care for participants with PHQ-9  $\geq 10$ .

If a participant endorses the self-harm item of the PHQ-9, a pop-up will immediately appear with instructions to call 911 or go to the nearest emergency room for a life-threatening emergency. Additionally, email triggers will immediately notify study staff, who will call to conduct a risk assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS).

At the beginning of the C-SSRS assessment, study staff will ask the participant for her current location. Study staff will provide psychological referrals for low to medium risk. For immediate risk, the study staff will direct the participant to the nearest emergency room and/or to call 911. If the participant declines, the study staff will call the participant’s local emergency services number, which will be recorded in the participant tracking database at enrollment. Study staff will immediately notify co-mentor Dr. Krystal, a psychiatrist with experience working with depressed and suicidal individuals, anytime a participant endorses suicidality on the PHQ-9. He will provide further supervision as deemed necessary and will determine whether additional follow-up assessment is indicated. Principal Investigator Dr. Felder, a licensed clinical psychologist with experience working with depressed perinatal women, will be a back-up if Dr. Krystal is unavailable.

Because suicidal impulses can change rapidly, participants will be instructed to make immediate contact with study personnel with any issues, questions, or concerns regarding worsening symptoms. At enrollment, we will provide contact information for Dr. Felder, Dr. Krystal, local therapeutic resources, and crisis hotlines so that participants can have the phone numbers readily accessible.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse events from the UCSF Clinical Research HUB: Adverse events are events that are undesirable and unintended, although not necessarily unexpected, effect of the research occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A Serious Adverse Event is defined as any Adverse Event that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

The events below are considered expected and will not be reported to the IRB:

- Increased sleepiness, which is a common short-term side effect of the sleep consolidation component of MBSR+PS
- Poorer sleep quality, which is normative as pregnancy advances

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

### 8.3.3.1 SEVERITY OF EVENT

Adverse events will be assessed by the principal investigator with co-investigator Dr. Krystal, who has experience assessing psychiatric adverse events, and/or co-investigator Dr. Hecht, who has experience assessing medical adverse events. The following guidelines will be used to describe severity.

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely related:** An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.
- **Probably related:** An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- **Possibly related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- **Unrelated:** The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated. Often, the cause of an unrelated AE is disease progression.

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### 8.3.3.3 EXPECTEDNESS

An AE that may be reasonably anticipated to occur as a result of the study procedures or study participation and should thus be described in the research proposal, the informed consent document, or is part of the normal disease process or progression. An AE or suspected adverse reaction is considered "unexpected" if it is unlikely to occur in the study population, or it is unlikely to occur at the severity that has been observed.

An adverse event is defined as being unexpected if the event exceeds the nature, severity or frequency described in the current IRB Application including the protocol and consent form. An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to a deviation from the IRB approved study protocol

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### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel when participants complete the adverse event questionnaire or when participants spontaneously report adverse events.

All AEs, not otherwise precluded per the protocol, will be captured on an adverse event report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

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

Dr. Felder will record events with start dates occurring any time after randomization until the last day of study participation. At endpoint, the investigator will inquire about the occurrence of AE/SAEs since randomization.

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### 8.3.5 ADVERSE EVENT REPORTING

Internal (on-site) adverse events that the PI determines to be 1. Definitely, probably or possibly related AND 2 Serious or unexpected will be reported to the IRB within 5 working days of UCSF PI awareness. Individual reports of AEs determined to be

unrelated to research participation will not be reported to the IRB. Instead, these events will be documented, referenced and retained in the PI's study files for follow-up.

The events below are considered expected and will not be reported to the IRB:

- Increased sleepiness, which is a common short-term side effect of the sleep consolidation component of MBSR+PS
- Poorer sleep quality, which is normative as pregnancy advances

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### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitoring Committee, UCSF IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the IRB, NCCIH Program Officer, and Independent Monitoring Committee immediately following the investigator's awareness of the event. Other serious and unexpected AEs related to the intervention will be reported within 5 working days of the investigator's awareness of the event.
- Individual reports of internal (on-site) AEs determined to be unrelated to research participation will not be reported to the IRB. Instead, these events will be documented, referenced and retained in the PI's study files for follow-up, and will be reported to NCCIH and the Independent Monitoring Committee on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitoring Committee. The Independent Monitoring Committee Report will state that all AEs have been reviewed.

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### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

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### 8.3.8 EVENTS OF SPECIAL INTEREST

N/A

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### 8.3.9 REPORTING OF PREGNANCY

N/A because pregnancy is an inclusion criterion for the study.

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## 8.4 UNANTICIPATED PROBLEMS

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### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the UCSF Institutional Review Board definition of Unanticipated Problems: An unanticipated problem is an unexpected, research-related event where the risk exceeds the nature, severity, or frequency described in the protocol, study consent form, or other study information previously reviewed and approved by the IRB.

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#### 8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the UCSF Institutional Review Board (IRB) and Independent Monitoring Committee (IMC). The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB, IMC, and to the funding agency within 5 working days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB, IMC, and to the funding agency within 10 days of the investigator becoming aware of the problem

The UP report will be completed by qualified study staff and reviewed and signed off by the Principal Investigator.

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#### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

## 9 STATISTICAL CONSIDERATIONS

### 9.1 STATISTICAL HYPOTHESES

Our primary objectives are to determine acceptability, feasibility, and adherence. We do not have formal hypotheses and descriptive statistics will be used to examine the metrics reported in the Section 3 table. A secondary objective is to explore group differences in change on potential mechanisms (e.g., psychological responses to nightly physical symptoms). Additionally, we will explore group differences in our primary clinical outcome, global sleep quality.

## 9.2 SAMPLE SIZE DETERMINATION

We did not use a power analysis to determine sample size because our focus is on examining acceptability, feasibility, and adherence, versus on statistical analyses of efficacy. We believe 40 participants is adequate to investigate these metrics. Based on our previous and ongoing research, we anticipate that retention at 8-weeks post-randomization will be  $\geq 80\%$ . Therefore, we will randomize 50 participants (50 randomized  $\times$  80% retention = 40 with 8-weeks post-randomization data).

## 9.3 POPULATIONS FOR ANALYSES

All analyses will be conducted on the intention-to-treat sample defined as all randomized participants. Secondly, analyses will be conducted on the per-protocol population of MBSR+PS participants who attended  $\geq 50\%$  sessions and all TAU participants.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

For descriptive statistics, categorical data will be presented with frequency and percentage. Continuous data will be presented with mean, standard deviation, median, and range. For exploratory inferential tests, statistical significance will be set at  $p < .05$ , and we will use 95% confidence intervals. Follow-up sensitivity analyses may include any factors that differed between groups at baseline.

### 9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The metrics used to calculate each endpoint are described in the Section 3 table. All primary endpoints will be examined descriptively.

#### **For the acceptability objective:**

- willingness to be randomized is binary
- treatment initiation is binary
- reasons for attrition is qualitative
- satisfaction scores are interval

#### **For the feasibility objective:**

- yield of eligible participants is interval
- number randomized is interval
- retention rate is interval

- completeness is interval
- missingness is qualitative

**For the adherence objective:**

- session attendance is interval
- home practice completion is interval

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#### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints are not dependent on findings of the primary endpoints. The metrics used to define each secondary endpoint are described in the Section 3 table.

The current study is not powered to examine between-group differences in change on psychological mediators, sleep, or other clinical outcomes, but analyses will be conducted to serve as preliminary data. Given that data are nested within participants (repeated measures) violating assumptions of independence, multilevel modeling (MLM) methods will be used to explore group differences (MBSR+PS vs. TAU) in change psychological mediators, sleep, and other clinical outcomes. Clustering at the group level will be included in the exploratory models, and we will calculate the intraclass correlation for clustering for future study planning. The strength of the relationship between change in each psychological mediator and improvement in subjective sleep quality will also be examined.

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#### 9.4.4 SAFETY ANALYSES

N/A

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#### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will collect the following baseline characteristics: age, race, ethnicity, highest level of education attained, income, marital status, number of children and their ages, zip code, insurance type, employment status, gestational age at enrollment. We will compare intervention groups using descriptive statistics.

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#### 9.4.6 PLANNED INTERIM ANALYSES

N/A

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#### 9.4.7 SUB-GROUP ANALYSES

Only adult females will be included in this study. We do not plan sub-group analyses.

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#### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point in any publications.

#### 9.4.9 EXPLORATORY ANALYSES

N/A

## 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

#### 10.1.1 INFORMED CONSENT PROCESS

##### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Participants will view the screening and study consent forms electronically and can download a PDF of the consent forms for their records. Consent forms describe in detail the study intervention, study procedures, and risks (see below). Prior to the beginning of the trial, we will receive the IRB's written approval for the protocol and the informed consent procedures and documents.

##### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Because this study involves no in-person visits, all consenting will occur electronically. There will be two consent forms: one describing the screening survey and one describing all other study procedures. Consent forms will be written at an eighth grade education level, use lay language, and will provide the following information: background and purpose of the study, scope and length of participation, randomization procedure, study procedures, follow-up assessments, legal and ethical limits to confidentiality, clinical interview audio and videotaping procedures, risks, benefits, alternatives, ability to discontinue participation, privacy and confidentiality, compensation, and whom to contact with questions. Women will be assured that their decision to participate or decline participation in the study will have no effect on their current or future receipt of healthcare services at UCSF or affiliated clinics. Women will be instructed to contact study staff with any questions, and will be able to download a copy of the consent forms for their records. For both consent forms, women will have the option to decline participation, consider their decision further, or provide their electronic signature to consent to participation. The orientation session provides another opportunity to engage participants in the informed consent process. In this session, study staff will meet by Zoom or phone to discuss the importance of the study question, the required commitments, what to expect if randomized to MBSR+PS or TAU, the rationale for random assignment, the consequences of attrition bias, and will answer

any questions that participants have.<sup>41</sup> All consent forms will be approved by the UCSF IRB prior to study commencement.

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### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

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

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### 10.1.3 CONFIDENTIALITY AND PRIVACY

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

Participants will be instructed to complete all research activities in as private a setting as possible (e.g., in a private room at home).

The Independent Monitoring Committee, authorized representatives of NCCIH, representatives of the Institutional Review Board (IRB) and regulatory agencies may inspect all documents and records required to be maintained by the investigator for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data will be collected and stored on online survey platforms Qualtrics and REDCap, and stored on Box, a collaborative cloud-based collaboration tool. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

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

One limit to confidentiality is if a woman indicates she is at imminent risk to harming herself. If a participant endorses the self-harm item of the PHQ-9, a pop-up will immediately appear with instructions to call 911 or go to the nearest emergency room for a life-threatening emergency. Additionally, email triggers will immediately notify study staff, who will call to conduct a risk assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS). At the beginning of the C-SSRS assessment, study staff will ask the participant for her current location. Study staff will provide psychological referrals for low to medium risk. For immediate risk, the study staff will direct the participant to the nearest emergency room and/or to call 911. If the participant declines, the study staff will call the participant's local emergency services number, which will be recorded in the participant tracking database at enrollment. Study staff will immediately notify co-mentor Dr. Krystal, a psychiatrist with experience working with depressed and suicidal individuals, anytime a participant endorses suicidality on the PHQ-9. He will provide further supervision as deemed necessary and will determine whether additional follow-up assessment is indicated. Principal Investigator Dr. Felder, a licensed clinical psychologist with experience working with depressed perinatal women, will be a back-up if Dr. Krystal is unavailable.

This study does not require the use of a Certificate of Confidentiality.

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#### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be stored on a cloud-based collaboration tool that uses access controls and encryption, and is safe for storing protected health information. Access will be limited to the PI and trained, authorized study staff. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Dryad data repository for use by other researchers including those outside of the study. We will receive a permanent DOI for our data through Dryad, and we will meet NCCIH and publisher requirements for data sharing. Permission to transmit data to Dryad will be included in the informed consent.

#### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

<b>Principal Investigator</b>	<b>Medical Monitor (Medical)</b>	<b>Medical Monitor (Psychiatric)</b>
Jennifer Felder, PhD, Assistant Professor and Principal Investigator	Rick Hecht, MD, Professor and Co-Investigator	Andrew Krystal, MD, Professor and Co-Investigator
University of California, San Francisco	University of California, San Francisco	University of California, San Francisco
Jennifer.Felder@ucsf.edu	Rick.hecht@ucsf.edu	Andrew.krystal@ucsf.edu

<b>Independent Monitoring Committee Member</b>	<b>Independent Monitoring Committee Member</b>	<b>Independent Monitoring Committee Member</b>
Norah Simpson, PhD, Clinical Associate Professor	Jane Kim, PhD, Clinical Assistant Professor	Judith Balk, MD
Stanford University	Stanford University	Self-employed
nsimpson@stanford.edu	janepkim@stanford.edu	judy_balk@icloud.com

#### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an Independent Monitoring Committee (IMC) composed of individuals with the appropriate expertise, including sleep during pregnancy, biostatistics, and obstetrics and gynecology. Members of the IMC will be independent from the study conduct and free of conflict of interest. The IMC will meet at least semiannually to assess safety and efficacy data from each arm of the study. The IMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the IMC. At this time, each data element that the IMC

needs to assess will be clearly defined. The IMC will provide its input to the National Institutes of Health staff.

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#### 10.1.7 CLINICAL MONITORING

N/A

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#### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

- **Informed consent:** Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.
- **Follow-up measures:** Self-report questionnaires will be designed to only accept valid responses. In real time and as close to data collection as possible, study staff will check each submitted self-report measure to identify and correct any potential issues (e.g., participant indicated on sleep diary that she went to sleep at 10:00 AM instead of 10:00 PM). Clinical research coordinators will make multiple attempts to contact participants to complete follow-up measures.
- **Intervention fidelity:** Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.
- **Protocol deviations:** The study team will review and document protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

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

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#### 10.1.9 DATA HANDLING AND RECORD KEEPING

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##### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of study staff under the supervision of the principal investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All data, including adverse events and use of non-study treatments, will be collected electronically using Qualtrics or REDCap. Each of these platforms encrypts all data, is HIPAA-compliant, and protects against data loss. Once downloaded, electronic data will

be stored on a cloud-based collaboration tool that uses access controls and encryption, and is safe for storing protected health information. Access will be limited to the PI and trained, authorized study staff.

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#### 10.1.9.2 STUDY RECORDS RETENTION

Per University of California policy regarding IRB and academic research records, study documents will be retained for a minimum of 10 years after the end of the calendar year in which the research is completed.

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#### 10.1.10 PROTOCOL DEVIATIONS

In accordance with UCSF IRB policy, this protocol defines protocol violations as changes in the conduct of an IRB-approved research protocol that are under the investigator's control and made without prior IRB approval. Incidents are any problematic or unanticipated events that are not protocol violations and that may adversely impact on the study participants or the conduct of the study.

Major (reportable) protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. All major violations will be reported to the IRB.

Major violations including, but not limited to incorrect intervention given, enrollment of ineligible participant, key safety procedure not done or done outside window, will be reported within 10 working days of awareness.

Immediate protocol changes to protect participant safety will be reported within 10 working days of occurrence.

Major incidents including, but not limited to problem with consent or recruitment process, significant complaint or concern, lapse in study approval, loss of adequate resources, potential breach of confidentiality of confidentiality, will be reported within 48 hours of awareness *if* they represent potential breaches of privacy or confidentiality. Other Major Incidents will be reported within 10 working days of awareness.

Minor protocol violations (also known as protocol deviations) are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB-approved protocol that do not have a major impact on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Minor protocol violations will not be reported to the IRB, but will be documented in the study files.

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#### 10.1.11 PUBLICATION AND DATA SHARING POLICY

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

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.
- After the study is completed, the de-identified, archived data will be transmitted to and stored at the Dryad data repository for use by other researchers including those outside of the study.

#### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. Conflicts of interest will be reported in the IRB application, all financial interest disclosures will be kept current with the UCSF Conflict of Interest Program office, and we will disclose any financial or proprietary interests in the consent form.

#### 10.2 ADDITIONAL CONSIDERATIONS

N/A

#### 10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTSI PRP	Clinical and Translational Science Institute Participant Recruitment Program
DOI	Digital Object Identifier

DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IMC	Independent Monitoring Committee
IRB	Institutional Review Board
ITT	Intention-To-Treat
MBCP	Mindfulness-Based Childbirth and Parenting
MBSR+PS	Mindfulness-Based Stress Reduction + Prenatal Sleep Supplement
MBSR	Mindfulness-Based Stress Reduction
MBTI	Mindfulness-Based Therapy for Insomnia
MOP	Manual of Procedures
MRN	Medical Record Number
NCT	National Clinical Trial
NCCIH	National Center for Complementary and Integrative Health
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PDF	Portable Document Format
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
QC	Quality Control
RCT	Randomized Clinical Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TAU	Treatment as Usual
UCSF	University of California, San Francisco
UP	Unanticipated Problem
US	United States

#### 10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
V2	4/21/21	Revise intervention to be mindfulness-based stress reduction plus prenatal sleep sessions	To pilot test an intervention that is maximally potent and that will fit into the existing delivery system.
V3	11/8/21	<ul style="list-style-type: none"> <li>5. Include MBSR classes that are offered at locations in addition to UCSF Osher Center</li> <li>6. Add recruitment sources</li> <li>7. Remove Epworth Sleepiness Scale</li> <li>8. Increase the gestational age range from 12-28 to 8-28.</li> </ul>	<p>5. A significant challenge is that the UCSF Osher Center does not offer MBSR frequently, and the classes fill up quickly. Currently, the number of eligible RISE Study participants exceeds the available spots in the Osher MBSR class. Additionally, we have had otherwise eligible study participants who were unable to participate because they were not available at the particular time of the Osher MBSR class</p>

			<p>6. To enable rapid identification of eligible participants and to maximize likelihood that we can achieve our anticipated accrual rate. We are having a lower yield from our Facebook ads compared to our previous studies. We are adding recruitment sources that we found helpful in previous studies, such as parenting listservs and social media posts</p> <p>7. Initially we planned to use the Epworth to screen for narcolepsy. The Epworth has excluded 10% of respondents on our screener. Narcolepsy has a base rate of 0.05%. Thus, it is highly implausible that 10% of respondents had narcolepsy. Instead we believe the Epworth is identifying people with normative pregnancy-related sleepiness. Additionally, this measure is redundant with an item that assesses whether participants have been diagnosed with narcolepsy</p> <p>8. We have had several potential participants who are experiencing significant sleep disruption, are</p>
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			interested in participating, but are less than 12 weeks pregnant (and will be too far along in their pregnancy for the next available MBSR course). This wider gestational age range is similar to our previous research, in which we evaluated digital CBT for prenatal insomnia, and enrolled participants at any point in pregnancy up until 28 weeks
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