Protocol

Perinatal Research on Improving Sleep and Mental health (PRISM) Study

National Clinical Trial (NCT) Identified Number: TBD

Principal Investigator: Jennifer Felder, PhD

Sponsor: University of California, San Francisco

Grant Title: Efficacy of digital cognitive behavior therapy for insomnia for the prevention of perinatal depression

Grant Number: R01MH126040

Funded by: National Institute of Mental Health

Version Number: 1.0

September 2, 2022

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

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

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

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

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent forms 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 forms 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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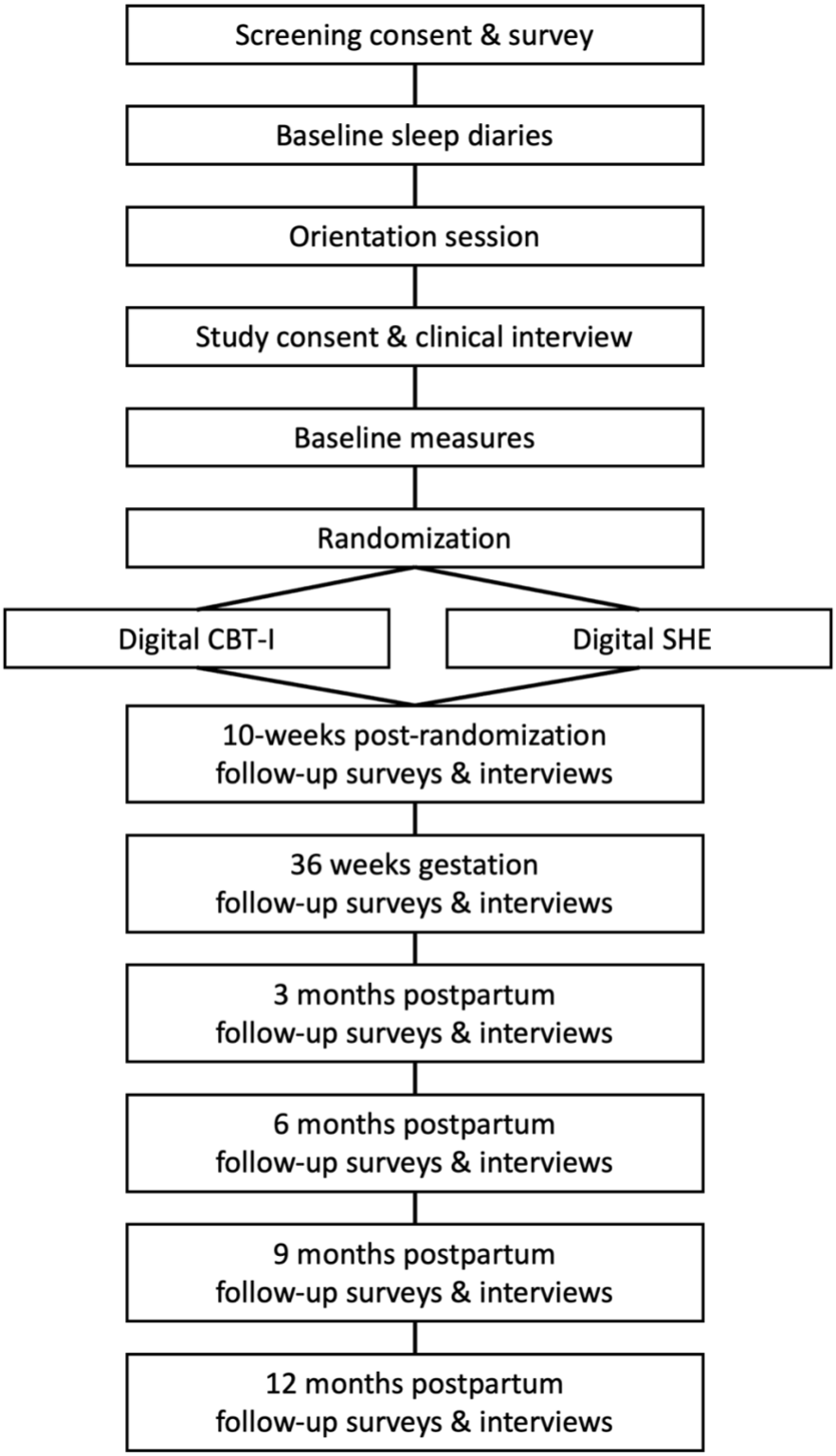
1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Grant Title:	Efficacy of digital cognitive behavior therapy for insomnia for the prevention of perinatal depression
Grant Number:	R01MH126040
Study Name:	Perinatal Research on Improving Sleep and Mental health (PRISM) Study
Study Description:	The PRISM Study is a blinded randomized controlled trial to evaluate the efficacy of digital CBT-I for the prevention of depression during pregnancy and through 12 months postpartum among 498 non-depressed people with insomnia disorder relative to a credible, clinically-relevant control condition.
Objectives:	• *Primary Objective*: To evaluate the efficacy of digital CBT-I for preventing perinatal depression; • *Secondary Objectives*: To test whether the effect of digital CBT-I on perinatal depression is mediated through prenatal insomnia symptom improvement; To test whether the effect of digital CBT-I on perinatal depression is moderated by baseline depressive symptom severity.
Endpoints:	• *Primary Endpoint*: Depression incidence; Change in depression symptom severity • *Secondary Endpoints*: Suicidal ideation; Change in anxiety symptom severity; Change in prenatal insomnia as a mediator; Baseline depressive symptom severity as a moderator
Study Population:	498 non-depressed pregnant people with insomnia disorder
Phase:	Confirmatory efficacy
Description of Sites:	Single site study at University of California, San Francisco
Description of Study Interventions:	• The *study intervention* is digital cognitive behavioral therapy for insomnia (CBT-I) from Big Hlth, Ltd, called Sleepio. This program involves 6 weekly sessions of 10-20 minutes each. The intervention also includes supplemental materials about prenatal, postpartum, and infant sleep. • The *control condition* is digital sleep hygiene education, a credible, clinically-relevant comparator that matches digital CBT-I in delivery format (digital), frequency (weekly), and number of sessions (six).
Study Duration:	4.25 years
Participant Duration:	Until 1 year postpartum; up to 18 months

1.2 SCHEMA


Screening consent & survey
Baseline sleep diaries
Orientation session
Study consent & clinical interview
Baseline measures
Randomization
Digital CBT-I
Digital SHE
10-weeks post-randomization
follow-up surveys & interviews
36 weeks gestation
follow-up surveys & interviews
3 months postpartum
follow-up surveys & interviews
6 months postpartum
follow-up surveys & interviews
9 months postpartum
follow-up surveys & interviews
12 months postpartum
follow-up surveys & interviews

1.3 SCHEDULE OF ACTIVITIES

	Screen. survey	***Screen. intvw.***	***Base.***	***5 w p-r***	***10 w p-r***	***36 w gest.***	***3 m pp***	***6 m pp***	***9 m pp***	***12 m pp***
Allowable window*	Up to 1 month before rand.	Up to 1 month before rand.	Up to 2 weeks before rand.	+/- 7 days	+/- 7 days	+/- 7 days	+/- 1 month	+/- 1 month	+/- 1 month	+/- 1 month
Miscellaneous measures										
Demographics	X									
Documentation of pregnancy	X									
TEQ*										
Birth date survey*										
Non-study treatment intvw.		X			X	X	X	X	X	X
Adverse events intvw.					X	X	X	X	X	X
CSQ					X					X
Exit survey					X					X
Primary clinical outcome measures										
SCID (primary)		X			X	X	X	X	X	X
EPDS			X	X	X	X	X	X	X	X
PHQ-9			X	X	X	X	X	X	X	X
Secondary clinical outcome measures										
C-SSRS		X			X	X	X	X	X	X
GAD-7			X		X	X	X	X	X	X
Birth outcomes							X			
Primary mediator measures										
ISI (primary)	X		X	X	X	X	X	X	X	X
SCISD		X			X	X	X	X	X	X
Sleep diary	X				X					
PSQI			X		X	X	X	X	X	X
Secondary mediator measures										
PTQ			X		X	X	X	X	X	X
DBAS-16			X		X	X	X	X	X	X
PSAS			X		X	X	X	X	X	X
DERS-SF			X		X	X	X	X	X	X
Maternal-infant outcomes										
BISQ-R							X	X	X	X
IBQ-R							X	X	X	X
MPAS							X	X	X	X

Abbreviations. Screen.=Screening survey; Intvw.=Interview; Orient.=orientation; Base.=Baseline; w=weeks; p-r=post-randomization; rand.=randomization; m=months; gest.=gestation; pp=postpartum; TEQ=Treatment Credibility and Expectancy Questionnaire; CSQ=Client Satisfaction Questionnaire; SCID=Structured Clinical Interview for DSM-5 Disorders; EPDS=Edinburgh Postnatal Depression Scale; PHQ-9=Patient Health Questionnaire; C-SSRS=Columbia Suicide Severity Rating Scale; GAD-7=Generalized Anxiety Disorder Scale; ISI=Insomnia Severity Index; SCISD=Structured Clinical Interview for DSM-5 Sleep Disorders; PSQI=Pittsburgh Sleep Quality Index; PTQ=Perseverative Thinking Questionnaire; DBAS=Dysfunctional Beliefs About Sleep scale;

PSAS=Pre-sleep Arousal Scale; DERS-SF=Difficulties in Emotion Regulation Scale-Short Form; BISQ-R=Brief Infant Sleep Questionnaire – Revised; IBQ-R=Infant Behavior Questionnaire – Revised; MPAS=Maternal Postnatal Attachment Scale.
Notes.* **Allowable windows: For the 5 weeks post-randomization, 10 weeks post-randomization, and 36 weeks gestation timepoints, the preferred response window is +/- 7 days, but we will accept +/- 14 days in exceptional circumstances. The 36 weeks gestation timepoint will not be collected if < 7 days from the 10 weeks post-randomization timepoint. If we are unable to obtain information about the date the participant delivered her baby, the postpartum timepoints will be tied to her estimated due date that is provided at screening; **TEQ** will be completed at randomization; **Birth date survey** will be completed 3 weeks after a participant's expected due date.

2 INTRODUCTION

2.1 STUDY RATIONALE

Perinatal depression (i.e., during pregnancy or the postpartum period) is common and associated with long-lasting consequences, including increased risk of suicide, impairments in parenting, and immense societal costs.

Prenatal insomnia is a robust risk factor for perinatal depression: nearly 1 in 4 women who experience prenatal insomnia develop postpartum depression. To date, no trials have investigated whether treating prenatal insomnia prevents perinatal depression. Digital cognitive behavior therapy (CBT-I) is safe and effective for treating prenatal insomnia and shows promise for preventing perinatal depression relative to standard care. Further, digital CBT-I may be of particular interest for pregnant women because it minimizes wait time, avoids burdensome traveling and scheduling requirements, and meets their preferences for flexible delivery options.

The proposed project is a blinded randomized controlled trial to evaluate the efficacy of digital CBT-I for the prevention of depression during pregnancy and through 12 months postpartum among 498 non-depressed women with insomnia disorder relative to a credible, clinically-relevant control condition. Consistent with other research, sleep hygiene education will be the control condition, and will match digital CBT-I in delivery format (digital), frequency (weekly), and number of sessions (six). The proposed confirmatory efficacy trial addresses three specific aims: 1) To evaluate the efficacy of digital CBT-I for preventing perinatal depression; 2) To test whether the effect of digital CBT-I on perinatal depression is mediated through prenatal insomnia symptom improvement; 3) To test whether the effect of digital CBT-I on perinatal depression is moderated by baseline depressive symptom severity.

2.2 BACKGROUND

Approximately 1 in 7 women experience depression during the perinatal period (i.e., during pregnancy or postpartum), making it the most common complication of childbirth.[1] Perinatal depression is associated with long-lasting consequences, including increased risk of suicide,[2] impairments in parenting,[3] and immense societal costs due to productivity loss, increased use

of welfare and Medicaid services, and higher health care expenditures.[4] Preventing perinatal depression may avert the long reach of these negative consequences.

Prenatal insomnia is a robust, yet modifiable, risk factor for perinatal depression.[5-7] Nearly 25% of women with prenatal insomnia develop postpartum depression.[7] Our recent randomized controlled trial (RCT) showed that digital cognitive behavior therapy for insomnia (CBT-I) is effective for treating prenatal insomnia.[8] A post-hoc analysis revealed that **6%** who were randomized to CBT-I experienced high perinatal depression symptoms compared to **22%** randomized to standard care (Cohen's H = 0.5). Based on these promising post-hoc findings, we will conduct a confirmatory efficacy trial sufficiently powered and designed to provide definitive evidence about whether treating prenatal insomnia prevents perinatal depression. This project will also provide valuable information about *how* and *for whom* CBT-I prevents perinatal depression. Based on our preliminary data, we will test the hypotheses that improvements in prenatal insomnia symptoms mediate the effect of digital CBT-I on perinatal depression, and that baseline depressive symptom severity moderates the effect.

As in our previous trial,[8] we will use digital, rather than therapist-led, CBT-I because demand for CBT-I exceeds the availability of trained clinicians,[9] and digital CBT-I minimizes wait time, avoids burdensome traveling and scheduling requirements, and meets pregnant women's preferences for flexible delivery options.[10] The digital CBT-I intervention is an interactive, fully automated program that is delivered by an animated therapist over six weekly sessions via a website or app.[11,12]

We will conduct a blinded RCT to evaluate the efficacy of digital CBT-I for the prevention of depression through 12 months postpartum compared with a credible, clinically-relevant comparator group. We will enroll 498 non-depressed pregnant women with insomnia disorder. We will use sleep hygiene education as the control condition, and it will match digital CBT-I on delivery format (digital), frequency (weekly), and total number of sessions (six). The content for our sleep hygiene education intervention has been used as a control condition in previous RCTs, and was rated as credible as CBT-I.[13] We investigate the following aims:

Aim 1: Evaluate the efficacy of digital CBT-I for preventing perinatal depression. Participants randomized to digital CBT-I will have significantly lower rates of incident major depression during the perinatal period (Hyp 1a) and lower depressive symptoms from baseline to 12 months postpartum (Hyp 1b) relative to participants randomized to digital sleep hygiene education.

Aim 2: Test mediators of the effect of digital CBT-I on perinatal depression. Change in prenatal insomnia symptom severity will mediate the effect of digital CBT-I on perinatal depression incidence (Hyp 2a) and perinatal depressive symptom severity (Hyp 2b). Secondary mediators include perseverative negative thinking, dysfunctional beliefs about sleep, nocturnal cognitive arousal, and emotion regulation.

Aim 3: Test moderation of the effect of digital CBT-I on perinatal depression. Baseline depressive symptom severity will moderate the effect of digital CBT-I on perinatal depression

incidence (Hyp 3a) and depressive symptom severity from baseline to 12 months postpartum (Hyp 3b).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Digital CBT-I. The sleep restriction component of CBT-I is designed to reduce the amount of time spent awake in bed, and to decrease sleep onset latency and wake after sleep onset by leveraging increased sleep drive. Participants may experience temporary increases in sleepiness during this component of treatment. Our previous trials of therapist-delivered and digital CBT-I among pregnant women found no unanticipated serious adverse events. We are aware of no other research to suggest that digital CBT-I would confer risk to fetal, obstetric, or infant outcomes.

Digital SHE. SHE is a credible control condition and is a clinically relevant comparator, as it is frequently used in clinical care. As a stand-alone treatment, it has low efficacy for improving insomnia. Therefore, we expect that women randomized to SHE will not experience significant improvements in insomnia and will continue to experience associated impairments in functioning and distress. We know of no other potential risks.

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 insomnia and depression symptoms.

Privacy of participants. Participants will complete study procedures and outcome measures remotely at a location that feels safe and private to them, which mitigates concerns about privacy. We address protections against privacy risk below in **Section 2.3.3**.

Worsening depressive symptoms and/or suicidal ideation. As is true for non-perinatal individuals generally, participants with insomnia may experience increases in depressive symptoms and/or suicidal ideation. Although we do not expect these to be research-related risks, there is the risk that the study team may observe worsening depressive symptoms and/or suicidal ideation.

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. There are also limits to confidentiality, such as if the study team observes possible evidence of child abuse, elder abuse, or a threat to self or others that we are required to report.

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

2.3.2 KNOWN POTENTIAL BENEFITS

Our previous data provide a strong empirical basis to predict reduction of insomnia symptoms and to suggest benefit for depression among women randomized to digital CBT-I. Participants may benefit from ongoing monitoring of and referral for depression incidence or suicidality. The minimal risks participants may experience in this study are reasonable in relation to anticipated benefits for those assigned to digital CBT-I. In the long-term, there are substantial benefits to be gained by evaluating digital CBT-I for the prevention of perinatal depression.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We will ask all participants to notify 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.

Digital CBT-I. Participants will be provided with a thorough description of the intervention prior to randomization. They will be informed that they can withdraw participation at any time without penalty.

Given our previous RCTs, we expect that digital CBT-I will be associated with improved insomnia and depression outcomes for some participants. However, important precautions will be taken to minimize risks associated with sleep deprivation. Specifically, participants will be instructed to keep their time in bed prescription ≥ 6 hours during the sleep restriction component of treatment.

Digital SHE. As with digital CBT-I, participants will be provided with a thorough description of the intervention prior to randomization and informed that they can withdraw participation at any time without penalty.

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 and clinical interview that skipping questions that are necessary for determining eligibility may preclude their ability to participate in the study.

Privacy of participants. We will display recruitment ads on social media platforms. People who are interested in participating will provide consent prior to completing the online screening survey. Participants will be reminded to complete all study activities, including completing study measures, clinical interviews, and digital intervention sessions, at a time and location that is private. We will report only de-identified data in study manuscripts.

Worsening depressive symptoms and/or suicidal ideation. Participants will be instructed to make immediate contact with study personnel with any questions or concerns regarding worsening depression symptoms or suicidal ideation. At enrollment, we will provide contact information for Dr. Krystal, Dr. Felder, therapeutic resources, and crisis hotlines.

Depression incidence will be monitored via clinical interviews at 6 timepoints after randomization. When a participant has an EPDS score > 9 or PHQ-9 score > 9, they will automatically view information for mental health resources. Additionally, email triggers will

notify study staff. Study staff will conduct the SCID to determine if the participant meets criteria for a major depressive episode. Study staff will recommend that any participant who meets criteria for a major depressive episode or who scores above the EPDS or PHQ-9 cutoff notify her obstetrician or primary care provider.

Suicidal ideation also will be monitored via self-report surveys and interviews at 6 timepoints after randomization. When a participant has an EPDS item 10 score > 0 or PHQ-9 item 9 > 0, they will complete the C-SSRS self-report, and automatically view information for suicide and mental health resources. Additionally, email triggers will notify study staff, who will follow our suicide risk assessment protocol. Please see the following documents for greater detail about the suicide risk assessment and response protocol: Suicide Ideation Response Flow and C-SSRS Response Scripts.

Confidentiality of data. All data will be handled with the utmost attention to participants' confidentiality. For more information, see ***Section 11.1.3***.

Inconvenience. Every effort will be taken to reduce participant burden, and we will accommodate participants' work and childcare constraints when scheduling interviews. Participants will be compensated $50 per timepoint for the time to complete self-report measures and clinical interviews.

Ensuring necessary intervention in the event of adverse events. Participants will be instructed to immediately inform their obstetrician or primary care physician if they experience any adverse events to determine whether intervention is needed. The study team will document, investigate, and follow-up all possible study-related AEs.

Plans for handling incidental findings. It is possible we may detect a previously undiagnosed psychiatric or sleep disorder during the clinical interviews. We will advise that participants follow-up with a medical or mental health care provider for further assessment.

The potential risks of participating in this study are minimal. Our previous research showed that digital CBT-I was associated with improved insomnia, depression, and anxiety during pregnancy and the postpartum period. All participants may benefit from ongoing monitoring of depression incidence or suicidality. In the long-term, there are substantial benefits to be gained by examining whether treating prenatal insomnia prevents perinatal depression.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the efficacy of digital CBT-I for preventing perinatal depression relative to digital SHE.	Depression incidence during the perinatal period (**Hypothesis 1a**) and depressive symptom severity from baseline to 12 months postpartum (**Hypothesis 1b**).	This endpoint was selected based on our preliminary data.
Secondary		
To evaluate the efficacy of digital CBT-I for improving secondary clinical outcomes relative to digital SHE.	Suicidal ideation and anxiety symptom severity from baseline to 12 months postpartum.	We selected these endpoints in response to the FOA, which strongly encourages assessment of suicidal behavior, and because perinatal insomnia and depression are associated with suicidal ideation[14] and anxiety[15,16]
To test mediators of the effect of digital CBT-I on perinatal depression.	Change in prenatal insomnia symptom severity as a mediator of the effect of digital CBT-I on perinatal depression incidence (**Hypothesis 2a**) and perinatal depressive symptom severity (**Hypothesis 2b**).	This endpoint was selected based on our preliminary data.
To test moderation of the effect of digital CBT-I on perinatal depression.	Baseline depressive symptom severity as a moderator of the effect of digital CBT-I on perinatal depression incidence (**Hypothesis 3a**) and depressive symptom severity (**Hypothesis 3B**).	This endpoint was selected based on our preliminary data.
Exploratory		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To explore the effect of digital CBT-I on gestational length relative to digital SHE.	Gestational length	This endpoint was selected based on data showing that insomnia and poor sleep quality are associated with increased risk of preterm birth.
To explore mediators of the effect of digital CBT-I on perinatal depression.	Psychological mediators of the effect of digital CBT-I on depression incidence during the perinatal period and depressive symptom severity from baseline to 12 months postpartum. Endpoints include Perseverative negative thinking; Dysfunctional beliefs about sleep; Nocturnal arousal; Emotion regulation deficits.	We selected measures that have been shown to mediate either the effect of CBT-I on depressive symptoms, or the relationship between insomnia and depression and that may be impacted by digital CBT-I.

4 STUDY DESIGN

4.1 OVERALL DESIGN

HYPOTHESIS

The primary goal of this confirmatory efficacy trial is to provide definitive evidence about whether treating prenatal insomnia prevents perinatal depression. Secondarily, we will explore evidence of whether the effect of digital CBT-I on perinatal depression is mediated through prenatal insomnia symptom improvement. Finally, we will test whether the effect of digital CBT-I on perinatal depression is moderated by baseline depressive symptom severity.

TRIAL DESIGN

This is a single-site, randomized controlled trial comparing CBT-I to SHE.

RANDOMIZATION

We will randomize participants to CBT-I or SHE after the baseline assessment using a 1:1 allocation ratio with blocked randomization to balance the group sizes. See **section 6.3** for more detail.

DURATION AND ARMS

The study will have two arms: digital CBT-I and digital SHE. There will be six follow up time points after randomization, and participation will end at 12 months postpartum.

INTERVENTIONS

Section 6.1 describes the intervention and control conditions in greater detail. In brief, cognitive behavioral therapy for insomnia (CBT-I) is our intervention condition. We use digital CBT-I program called Sleepio (Big Health, Ltd), which is delivered through a webpage or app in six 10-20 minute weekly sessions.

Sleep hygiene education (SHE) is our control condition. SHE matches digital CBT-I on delivery format (digital), frequency (weekly), and total number of sessions (six). The content for SHE has been used as a control condition previous RCTs.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Our research question is whether digital CBT-I outperforms a clinically-relevant comparator. SHE has face validity, is frequently used in clinical practice,[17,18] and is rated as credible as CBT-I.[13] We considered using the control from Dr. Manber's previous trial and decided against it for two primary reasons: 1) it is not used in clinical practice and therefore does not address our research question, and 2) it contains several active components included in our study intervention, such as information about healthy sleep habits, information about sleep and sleep during pregnancy, and education about infant sleep development; use of this control condition would decrease our ability to accurately determine the effects of digital CBT-I.

4.3 JUSTIFICATION FOR INTERVENTION

The digital CBT-I program we will use is called Sleepio (Big Health, Ltd). We used Sleepio in our previous trial showing that digital CBT-I is effective tor treating prenatal insomnia.[8,19] At the time, Sleepio was the only digital CBT-I option that was a stand-alone computer- and app-based intervention. We expected that some women would prefer to complete the intervention on their phone or tablet, and that a computer-only intervention would limit access.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study upon completion of the 12-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

The trial is considered completed when participants are no longer being followed or the last participant's last study visit has occurred.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants complete a consent form describing the screening procedures, and a study consent form describing study procedures. Participants are considered enrolled after they are randomized. Individuals must meet all of the following inclusion criteria in order to be eligible to participate:

Inclusion criteria	Rationale	Ascertainment
Pregnant 14-28 weeks gestation	Women who experience a miscarriage will become ineligible and will be withdrawn. We chose the lower limit of 14 weeks because the rate of first trimester miscarriage in women with a missed menstrual period and positive urine pregnancy test is 12-24%,[20] and the upper limit of 28 weeks so women have time to complete the interventions prior to birth.	Self-report; Documentation of pregnancy (e.g., dated ultrasound image, after visit summary)
18 years or older	Adolescents have unique sleep needs.	Self-report
Daily access to a web-enabled computer, smart phone, or tablet	Interventions will be delivered digitally, and the sleep diary requires daily monitoring of sleep via online surveys. In 2019, over 90% of adults ages 18-49 had a smart phone and 77% had broadband internet at home; 91% of women 18-49 years old with low income had a smartphone or high-speed broadband internet at home, thus mitigating concerns that requiring daily internet access will exclude individuals with low income.[21]	Self-report
Current elevated insomnia symptom severity and insomnia disorder	We will include women who are likely to meet criteria for insomnia disorder using a cut-off of 11 on the ISI, which has been validated for identifying participants in clinical trials.[22] Insomnia disorder is an inclusion criteria because CBT-I is indicated for insomnia disorder.[23]	Insomnia Severity Index ≥ 11; Structured Clinical Interview for DSM-5 Sleep Disorders (SCISD)[24]
English speaking	The digital CBT-I app is currently available in English only.	Self-report

5.2 EXCLUSION CRITERIA

Individuals meeting any of the exclusion criteria below will be excluded from study participation:

Exclusion criteria	Rationale	Ascertainment

Current major depression	Our focus is on preventing, not treating, perinatal depression.	Structured Clinical Interview for DSM-5, Research Version (SCID)[25]
Taking or planning to take antidepressant medication (ADM)	ADM use would make the effect of CBT-I on preventing depression difficult to interpret.	Self-report
Other diagnosed or suspected sleep disorder	We will exclude sleep disorders not likely to benefit from digital CBT-I.	SCISD; validated screeners for prenatal sleep apnea[26]
Other psychiatric or medical issues (e.g., bipolar disorder, active suicidality, bed rest)	We will exclude people who have any psychiatric or medical issues that necessitate priority treatment, could be exacerbated by the sleep restriction component of CBT-I, or would interfere with participation.	SCID; Columbia-Suicide Severity Rating Scale; Self-report
Night shift worker	CBT-I would likely be ineffective, or the effect would be difficult to interpret.	Self-report

5.3 LIFESTYLE CONSIDERATIONS

There are no restrictions related to lifestyle.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently randomized. 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.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

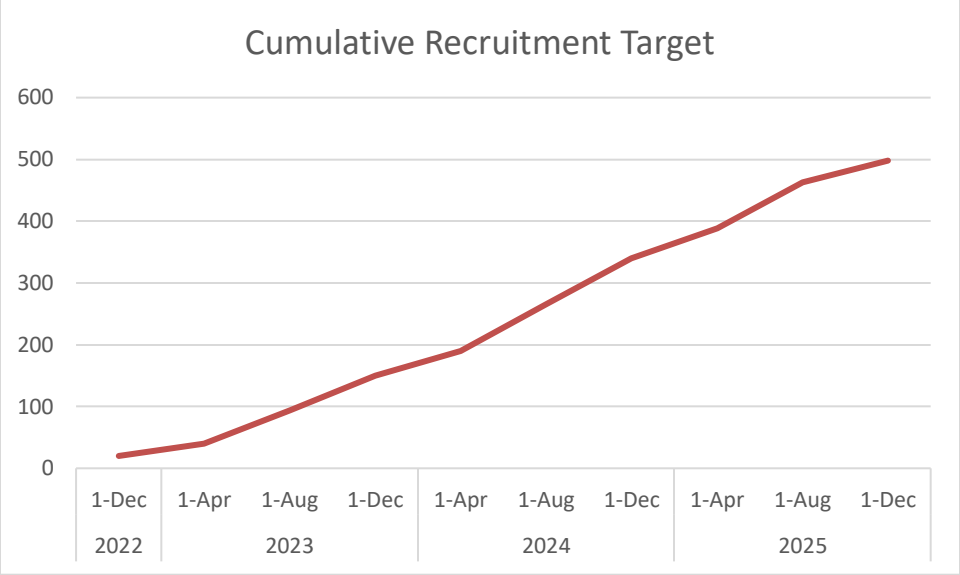
ANTICIPATED NUMBER TO BE SCREENED

Based on our previous trial, we anticipate we will need to screen approximately 5,500 people to randomize 498 participants.

ANTICIPATED ENROLLMENT SAMPLE SIZE BY GENDER, RACE AND ETHNICITY, AND AGE

All participants will be pregnant adults 18 years or older. Per our inclusion enrollment report, we plan to enroll 115 Hispanic or Latina people and 383 non-Hispanic or Latina people. We plan to enroll 6 American Indian/Alaska Native people, 32 Asian people, 5 Native Hawaiian or Other Pacific Islander people, 79 Black or African American people, 364 white people, and 12 multi-racial people.

ANTICIPATED ACCRUAL RATE OVER THE COURSE OF THE STUDY



RECRUITMENT AND REFERRAL SOURCES

As in our previous research, we will use online sources, such as Facebook and Ovia Pregnancy, to recruit 498 non-depressed pregnant women with insomnia disorder. Facebook is a global social network site. The Facebook audience selection tool suggests that there are currently 210,000 women in the United States whose behaviors on Facebook suggest they are pregnant and experiencing insomnia. In our previous trial of digital CBT-I, at least 1,600 of the people who completed our screening survey learned about the study from Facebook, and 74 ultimately enrolled in the study. In our previous trial of therapist-led CBT-I, we also had great success using targeted Facebook advertisements to recruit pregnant people with insomnia. Ovia Pregnancy is an app that provides clinical guidance, a personalized pregnancy timeline, and anonymous community to over 950,000 monthly active users. Users access the app an average of 21 times per month. Other investigators have used Ovia Pregnancy to successfully recruit research participants, including for an RCT of a digital depression prevention program.[27]

Other possible recruitment sources include:

Study website: Potential participants can view our study website (prismstudy.ucsf.edu) to learn more about the study or take the eligibility survey.

Clinicaltrials.gov: Potential participants can view our study information and click a button to request more information from study staff.

Word of mouth: People who view our ads may, with or without our awareness, share our study information. Thus, potential participants may learn about the study by word of mouth.

Our team has extensive experience recruiting pregnant women with insomnia using these sources and we are confident we can meet recruitment goals on time.[8,28] However, if we face enrollment shortfalls, we will utilize alternate online referral sources, such as::

Google Advertisements: Google AdWords is a pay-per-click online advertising platform that allows advertisers to display their ads on Google's search engine results page. Google ads have been used in previous research studies to recruit participants.

Other online sources: We will identify blogs, Reddit pages, listservs, websites, Facebook pages, Twitter accounts, Instagram accounts, and Pinterest accounts that serve the population we are targeting for recruitment (e.g., pregnant people) to host IRB-approved ads. Advertisements will include IRB-approved recruitment text with a brief description of the study, study contact information, and a link to the online eligibility survey.

Conventional, Passive Recruitment: Study ads will be posted in community, medical, and retail settings serving a high volume of people (e.g., coffee shops, grocery stores, etc.), women who are pregnant (e.g., WIC, Black Infant Health, maternity clothing stores, etc.), and families (e.g., toy stores).

Recruitment of under-represented minority groups is critical to obtain accurate and useful outcome data. To ensure that under-represented minorities are enrolled, we will work with the NIH-funded Clinical and Translational Awards' (CTSA) Participant Recruitment Program (PRP) at UCSF. PRP provides tools, resources, and services to support enrollment of under-represented populations. We will partner with the PRP to:

- Develop culturally concordant recruitment materials for under-represented populations by partnering with community members through the PRP's Virtual Feedback Advisory Board. Community members will provide feedback on images, text, and overall user experience of the recruitment materials.
- Engage the PRP Plain Language Consultation Service to ensure that recruitment advertisements, study website, and screening materials are accessible to a wide range of literacy levels.
- Engage a PRP social media recruitment specialist with expertise in recruiting under-represented minorities.

If we begin to fall short of planned inclusion targets, we will convene a work group, comprised of three members from the UCSF Preterm Birth Initiative Community Advisory Board (PTBi CAB) who are women of color dedicated to improving reproductive health equity. The work group will meet quarterly to assist with our efforts to enroll under-represented populations by providing feedback on study recruitment materials, the enrollment process, and study

materials. If needed, they will help us expand our recruitment efforts to community-based organizations that primarily serve women of color in San Francisco, Oakland, and Fresno.

Finally, we will:

- Use advertisement images featuring racially and ethnically diverse pregnant women.
- Use targeted recruitment text (e.g., "Recruiting pregnant Latina women").
- Utilize Facebook's audience selection tool to display our ads in zip codes that have a higher proportion of racially and ethnically diverse populations.
- Offer flexible appointment times for interviews to accommodate a range of schedules.
- Employ study staff who are under-represented minorities.

PARTICIPANT IDENTIFICATION

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

PARTICIPANT TRACKING

As in our previous research, we will use a REDCap database to monitor enrollment by recruitment strategy to optimize our recruitment approach, and 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. REDCap is a HIPAA-compliant and secure web application designed for data capture for clinical research and trials.

PARTICIPANT RETENTION

We will employ several strategies that we believe contributed to high retention in our previous RCT of digital CBT-I:

- Use of daily sleep diaries as behavioral run-in
- Orientation session prior to enrollment to discuss the rationale and importance of the trial, the required commitment, what to expect if randomized to digital CBT-I or sleep hygiene, the rationale for random assignment, and the detrimental effects of attrition bias on the success of the study.[29]
- Recognizable project identity by use of a study logo, and similar colors and fonts on trial materials
- Protocols to address common participant questions
- Employ "gracious but tenacious" research assistants who can offer flexible schedules for conducting clinical interviews, and who will send reminders about interview appointments, and make multiple attempts to contact participants to complete follow-up measures.
- Request contact information for a back-up contact person who can help us locate the participant if we have trouble reaching them

- Send birthday cards and study branded baby onesies
- Participants will be compensated $50 for completing study surveys at each main timepoint (i.e., up to $350).

In our previous trial, retention rates were > 80% at each timepoint.

INCENTIVES

We will compensate research participants $50 upon completing the study surveys and clinical interview at each timepoint.

JUSTIFICATION FOR INCLUSION OF VULNERABLE PARTICIPANTS

We focus on the vulnerable population of pregnant people because we want to decrease the risk of depression during this critical lifecycle phase, and there are limited prevention interventions for non-depressed pregnant women with insomnia disorder. Our proposed study meets each of the Department of Health and Human Services conditions for involving pregnant women in research (section §46.204):

- Our previous trials found very few adverse events, and the unanticipated events that were detected were not likely to be related to participation in the study;
- Study interventions that may have potential, unforeseen risks to the fetus have the prospect of direct benefit for the woman;
- We believe that the risks are the least possible for achieving the research objectives;
- We will obtain informed consent;
- No inducements will be offered to terminate the pregnancy;
- Study staff will not be involved in decisions about pregnancy termination;
- Study staff will have no part in determining the viability of a neonate

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

INTERVENTIONS

The digital cognitive behavioral therapy for insomnia (CBT-I) program we will use is called Sleepio (Big Health, Ltd). Digital CBT-I will be delivered by an animated therapist in six weekly sessions that are approximately 10-20 minutes each. Sessions can be accessed via website, iOS app, or Android app at a time that is convenient for the participant. Session content is based on standard, in-person CBT-I protocols, and includes sleep consolidation, stimulus control, cognitive therapy, relaxation techniques, and sleep hygiene education. The program is interactive, automated, and tailored to participant progress. Participants receive reminders to complete each session, and have access to a moderated community of other users and to a

library of sleep information, including recommendations tailored for pregnant and postpartum women. Additionally, participants will receive supplemental content about prenatal, postpartum, and infant sleep, previously evaluated in Dr. Manber's trial of therapist-delivered CBT-I for prenatal insomnia. Content includes sleep hygiene recommendations specific for pregnancy, suggestions for improving postpartum sleep, instructions on how to adjust the time in bed prescription during the postpartum period, psychoeducation about infant sleep, and tips for promoting healthy sleep development among babies 0-3 months and 3-6 months of age.

The control condition is sleep hygiene education (SHE) that matches the CBT-I intervention in delivery format (digital), frequency (weekly), and number of sessions (six). It includes information about sleep hygiene, the impact of sleep on performance, healthy sleep habits, lifestyle influences on sleep, and creating a sleep-friendly bedroom.

INTENDED MECHANISTIC TARGET OF THE INTERVENTION

We examine insomnia symptom severity reduction as a mediator and explore secondary mediators including perseverative negative thinking; dysfunctional beliefs about sleep; nocturnal arousal; emotion regulation deficits.

6.1.2 ADMINISTRATION AND/OR DOSING

The full-dose digital CBT-I program consists of:

Sleepio (Big Health, Ltd):

- Content delivered in 6 weekly 10-20 minute sessions
- Accessed via website or app
- Accessed independently at a time and location that is convenient for the participant

Supplemental CBT-I content:

- Available as downloadable PDF files
- Prenatal content delivered upon starting Sleepio
- Postpartum and infant content delivered at 36 weeks gestation and 3 months postpartum

The full-dose digital SHE program will consist of:

- Content delivered in 6 weekly 10-20 minute sessions
- Accessed online
- Accessed independently at a time and location that is convenient for the participant

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The digital CBT-I program, Sleepio (Big Health, Ltd), is a standardized, automated program where the same content will be delivered to each participant in 6 weekly sessions.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Based on our previous research using this intervention with this population we do not expect to break the randomization code. At their discretion, the DSMB can break the randomization blind to protect participant safety if needed.

We will use a 1:1 allocation ratio with blocked randomization to balance the group sizes. The randomization sequence will be generated by the study biostatistician and a masked randomization table will be uploaded to the REDCap database. The randomization sequence and block sizes will be concealed from all other study team members and participants. Study team members will not be able to influence randomization. Once an eligible participant completes baseline measures, unmasked study staff will reveal the allocation assignment, and notify participants of their assigned condition.

The principal investigator and any staff member involved in conducting outcome assessments will be blinded from condition assignment. Although we cannot blind participants from condition assignment, allocation will occur after the participant has enrolled to avoid selection bias, and we will mitigate the effect of participant expectations by comparing two credible conditions. Interviewers will instruct participants to not reveal their study assignment during clinical interviews.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participant adherence to the intervention is defined as completion of the weekly sessions. Completion of digital CBT-I sessions is captured by Sleepio and shared with the study team. Completion of digital SHE sessions is captured by REDCap by the study team.

6.5 CONCOMITANT THERAPY

At each follow-up timepoint, we will assess use of non-study treatments (type, dose, frequency). We will conduct sensitivity analyses to examine whether study findings change substantively when omitting participants with non-study treatments.

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

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

The study intervention may be discontinued when the principal investigator believes that continuing the study intervention is not in subject's best interest, for safety or other reasons. This decision will be made in consultation with the study medical monitors.

When a subject discontinues from digital CBT-I or digital SHE but not from the study, the remaining study procedures will be completed as indicated by the study protocol.

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

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Participants with pregnancy loss or fetal demise or whose baby dies during the postpartum period will be withdrawn from the study. Otherwise, no randomized participants will be withdrawn to permit intention-to-treat analyses.

The reason for participant discontinuation or withdrawal from the study will be recorded.

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) 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 contact at each subsequent timepoint. Participants will not be withdrawn due to lost to follow-up at any timepoint.

8 STUDY ASSESSMENTS AND PROCEDURE

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

PROCEDURES

All study procedures are remote (e.g., surveys completed via REDCap, orientation and interviews completed via video-conferencing).

Screening survey. People interested in participating will complete an electronic consent form describing the screening survey, baseline sleep diaries, and orientation session. Those who consent to the screening process will then complete the online screening survey to determine potential eligibility. Those determined to be potentially eligible with next complete baseline sleep diaries.

Baseline sleep diaries. Each morning for 7 consecutive days, potential participants will receive a link to a brief online sleep diary. Sleep diaries will establish baseline sleep behaviors, such as sleep onset latency, wake after sleep onset, sleep duration, and sleep efficiency, prior to randomization. Additionally, they will serve as a behavioral run-in to identify women who are likely to complete study measures after randomization. Those who complete at least 4 of 7 sleep diaries will be invited to complete the orientation session.

Orientation session. In a video conference appointment, study staff will discuss the importance of the study question, the required commitments, what to expect if randomized to digital CBT-I or digital SHE, the rationale for random assignment, and the consequences of attrition bias. These appointments may be one-on-one or in a group. Women who decide to participate after the orientation session will be invited to complete the clinical interview.

Consenting and clinical interviews. Study staff will review the study consent form with participants. Those who consent to participate will complete clinical interviews to determine eligibility and fully characterize the sample.

Baseline measures. Participants will complete baseline measures via online survey prior to randomization. See the "Measures" section below.

Randomization and intervention. Participants will be randomized to digital CBT-I or digital SHE after completing baseline measures, and complete a brief measures of treatment expectations and credibility. See *6.1* for a description of the interventions.

Follow-up measures**.** At 5-weeks post-randomization, participants will complete brief online measures of insomnia and depressive symptom severity. Participants will complete follow-up measures via online surveys and clinical interviews via video-conferencing at 10-weeks post-randomization, 36 weeks gestation, and every three months after delivery (i.e., 3, 6, 9, and 12 months postpartum). These are described below in the "Measures" section.

MEASURES

See **Section 1.3** Schedule of Activities for an overview of the measurement schedule.

Screening measures. We will collect information about recruitment source, pregnancy status, and demographics, and assess several eligibility criteria (e.g., access to the Internet, ability to speak and read English, no history of bipolar disorder, etc.). Potential participants will be asked to submit *documentation of their pregnancy* (e.g., dated ultrasound image).

We will assess insomnia symptom severity using the *Insomnia Severity Index (ISI)*, a 7-item measure that assesses difficulty initiating or maintaining sleep, satisfaction with sleep, impairment, distress, and the extent to which others have noticed symptoms over the last two weeks.[30] The ISI had high internal consistency in a clinical sample seeking treatment for insomnia (Cronbach's alpha = 0.91). At screening, we will exclude women who are unlikely to meet criteria for insomnia disorder using a cut-off validated for identifying participants in clinical trials (ISI < 11).[22] This cut-off yielded 97% sensitivity and 100% specificity when compared to a semi-structured diagnostic interview.

We will use the *consensus sleep diary* to establish baseline sleep behaviors and to serve as a behavioral run-in.[31] The consensus sleep diary is the gold standard measure of subjective sleep, and was developed in part by co-Investigator Dr. Krystal. The psychometrics suggest that the consensus sleep diary is associated with subjective and objective measures of sleep, differentiates good sleepers from those with insomnia disorder, and is sensitive to improvements over the course of CBT-I treatment.[32] From the sleep diaries, we will compute average sleep onset latency, wake after sleep onset, sleep efficiency, and sleep duration.

To screen out women with probable sleep apnea, we will use a *validated pregnancy-specific screening tool for sleep apnea*,[26] which has sensitivity of 86% and specificity of 74% for the diagnosis of sleep apnea.

Eligibility interviews. We will use the *Structured Clinical Interview for DSM-5, Research Version* (SCID) to exclude women with current major depression and other psychiatric disorders that necessitate priority treatment, could be exacerbated by the sleep restriction component of CBT-I, or would interfere with participation, and to fully characterize the sample.[25]

We will use the *Columbia-Suicide Severity Rating Scale (C-SSRS)*, *Lifetime Recent*[33] version to exclude women with active suicidality in the past month or who have attempted suicide in the past 6 months.[13] It was developed with support by NIMH and is recommended by the Centers for Disease Control and Food and Drug Administration. Psychometric data indicate that the C-SSRS has convergent, divergent, and predictive validity, is sensitive to change, and has high internal consistency.[33]

We will use the *Structured Clinical Interview for DSM-5 Sleep Disorders (SCISD)* to include women with current insomnia disorder and to exclude women with other sleep disorders, such as restless legs syndrome, hypersomnia, circadian rhythm disorder, nightmare disorder, or suspected sleep apnea.[24] Inter-rater reliability was good to excellent for each of these disorders. In order to include women whose insomnia symptoms began during pregnancy, we will enroll women with either episodic (symptoms present 1-3 months) or persistent (symptoms present ≥3 months) insomnia, consistent with our previous trials of CBT-I for prenatal insomnia.[8,28]

Primary clinical outcome measures. We will use the depression module of the *SCID-5*, described in the "Eligibility interviews" section, to assess our primary clinical outcome, incidence of perinatal depression. This is a binary outcome that measures whether a participant experienced a depressive episode at any point since randomization. To reduce recall bias, we will conduct interviews at each follow-up timepoint (i.e., 10 weeks post-randomization, 36 weeks gestation, 3, 6, 9, and 12 months postpartum). The stem question will be revised from "in the last month, have you experienced…" to "since the last interview on [date], have you experienced…" This interview will also provide estimates of time to depression onset, and duration and severity of symptoms among participants who experience a depressive episode.

We will use the *Edinburgh Postnatal Depression Scale (EPDS)*[34] to quantify depressive symptom severity.[34] Participants will complete the EPDS at each follow-up timepoint, allowing us to measure changes in depressive symptoms from baseline to 12 months postpartum. The EPDS is a 10-item self-report measure that omits depressive symptoms that can be conflated with normal perinatal symptoms. It is frequently used and validated to assess depressive symptom severity during pregnancy,[35,36] with estimates of sensitivity and specificity for detecting major depression ranging from 70-100% and 74-97%, respectively, depending on cut-off and sample.[37] Among postpartum women, estimates of sensitivity and specificity are 86% and 78%, respectively.[34] We will also use the Patient Health Questionnaire (PHQ-9) to quantify depressive symptom severity.[38] This is a 9-item measure frequently used in research and clinical practice.

Secondary clinical outcome measures. We will assess suicidal ideation and anxiety because perinatal insomnia and depression are associated with suicidal ideation and [14] anxiety.[15,16] We will use the *C-SSRS, Since Last Contact* version to assess suicidal ideation, intensity of ideation, and suicidal behavior since the last interview, and provide appropriate referrals as needed (see "Protection of Human Subjects" section for more detail).

We will use the *Generalized Anxiety Disorder Scale (GAD-7)* to assess anxiety symptom severity.[39] Among pregnant and postpartum women, a cut-off of 13 on the GAD-7 has sensitivity of 61% and specificity of 73% for detecting diagnoses of generalized anxiety disorder.[40]

Exploratory clinical outcome measure. We will assess gestational length because perinatal insomnia and depression are associated with poorer birth outcomes.[41,42] We will use a self-report measure to assess *birth outcomes*. Research shows that women reliably self-report their birth outcomes when compared with medical record data.[43,44] At four months postpartum, maternal recall of birth outcomes had high agreement with medical record data: sensitivity and specificity were > 82% for caesarean delivery, epidural usage, infant gender, low birth weight, labor induction, multiple gestation pregnancy, post-term birth, and preterm birth.[43]

Primary mediator measure. We will use the *ISI*, described above in the "Screening measures" section, to assess our primary mediator, change in insomnia symptom severity. We selected the ISI as our primary mediator measure because we have preliminary data indicating target engagement and validation using this measure. We will also use the *consensus sleep diary* to assess sleep behaviors.

Exploratory mediator measures. We will assess perseverative negative thinking using the *Perseverative Thinking Questionnaire (PTQ)*,[45] which was shown to mediate the depression prevention effect of digital CBT-I in a non-perinatal population.[46] The PTQ has 15 items and total scores range from 0-60, with higher scores indicating greater tendency to engage in transdiagnostic repetitive negative thinking.[45,47] Among pregnant and postpartum samples, the PTQ demonstrates high internal consistency (α >=.95).[48,49]

We will assess dysfunctional beliefs about sleep using the brief *Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16)*,[50] which were shown to mediate reductions in depressive symptom severity via CBT-I in a non-perinatal population (18% variance explained).[51] The DBAS has 16 items and total scores range from 0-10, with higher scores indicating more dysfunctional beliefs and attitudes about sleep.[50] Among non-perinatal samples, the DBAS-16 demonstrates adequate internal consistency (α >=.77) and temporal stability (r=.83).[50]

We will assess cognitive and somatic manifestations of nocturnal arousal using the *Pre-sleep Arousal Scale (PSAS)*.[52] In a perinatal sample, nocturnal cognitive arousal was shown to mediate 23-43% of the effect of insomnia on depression.[53] The PSAS has 16 items and total scores for the two subscales range from 8-40, with higher scores indicating greater nocturnal arousal.[52]

We will use the *Difficulties in Emotion Regulation Scale-Short Form* (DERS-SF) to assess emotion regulation deficits.[54] In a non-perinatal sample, DERS scores mediated the effect of probable insomnia disorder on depressive symptoms (37% total effect mediated).[55] The DERS-SF has 18 items and 6 subscales, and the psychometric properties are at least comparable to the original full-length scale.[54,56] The Cronbach's alpha for the total score was 0.89 in an adult sample, with adequate concurrent validity.[54]

Moderator measure. We will use the *EPDS*, described above in the "Screening Measures" section, to assess our primary moderator, baseline depressive symptom severity. We selected baseline depressive symptom severity as our primary moderator based on our strong preliminary data, as well as similar findings in a non-perinatal population.[57]

Other measures. We will use the *Treatment Credibility/Expectancy Questionnaire* to measure expectations about the sleep program at randomization.[58] We will use the *Client Satisfaction Questionnaire* to measure satisfaction with the sleep program.[59] We will use a *birth date questionnaire* to assess the date a participant had her baby in order to determine when to send the postpartum follow-up questionnaires. We will use an *exit questionnaire* to collect information on participants' experiences with the program in order to inform future research**.** We will collect information about *use of non-study treatments* in an interview. We will collect information about *any adverse events* in an interview.

8.2 SAFETY ASSESSMENTS

Adverse events may be identified via the adverse events interview administered at each follow-up timepoint, via self-report questionnaires or interviews, or by other participant report. Upon identification of a possible adverse event, trained study staff will conduct an adverse event

interview to characterize the type and severity of the event and the relationship to the study intervention and study procedures. Dr. Krystal will review psychiatric events and Dr. Yeaton-Massey will review medical events. These medical monitors will advise on additional event assessment and follow-up.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Per the UCSF Human Research Protection Program, an adverse event is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Per the UCSF Human Research Protection Program, 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
- 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

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild:** Participant is aware of symptoms, but is able to tolerate them, and no to minimal intervention is required.
- **Moderate:** Participant experiences enough symptoms to require intervention.
- **Severe:** Participant experiences symptoms or findings that require significant intervention or is life threatening. Severity is not synonymous with seriousness.

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, per the UCSF Human Research Protection Program:

- **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.

8.3.3.3 EXPECTEDNESS

Per the UCSF Human Research Protection Program, expected adverse events are defined as those that may be reasonably anticipated to occur as a result of the study procedures or study participation 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 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

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

- COVID diagnosis
- Increased sleepiness, which is a common short-term side effect of the sleep consolidation component of CBT-I
- Events that are expected among individuals with insomnia, including worsening depressive or anxiety symptoms, and/or suicidal ideation
- Events that are expected during pregnancy, including but not limited to: depression, anxiety, worsening sleep quality, fatigue, gestational diabetes, hypertensive disorders, pregnancy loss including miscarriage and stillbirth, hyperemesis gravidarum, nausea or vomiting, increased susceptibility to infection (including urinary tract infection), vaginal

bleeding, preterm labor, premature rupture of amniotic sac, preterm delivery, cesarean delivery, operative vaginal delivery, induction of labor.

- Events that are expected during the postpartum period, including but not limited to: lacerations and stitches, pain, postpartum hemorrhage, hypertension and hypertensive disorders, sleep disturbances, depression, anxiety.

Individual reports of AEs determined to be unrelated to research participation will not be reported to the IRB. Instead, these events will be documented, retained in the study files, and reported to the DSMB on an annual basis.

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 via participant report on the adverse event interview, other study questionnaires, or via other participant report.

All AEs will be captured on the adverse event report form. Information to be collected includes event description, time of onset, severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs 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 signs the study consent form 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.

The study team will record events with start dates occurring any time after the study consent is signed until the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported to the UCSF IRB per the reporting requirements (*https://irb.ucsf.edu/adverse-event#Reporting-requirements-chart*). 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, DSMB, NIMH within 5 working days of UCSF PI awareness.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs that are unexpected, serious, and definitely, probably, or possibly related to the study intervention will be reported to UCSF IRB and DSMB in accordance with the reporting requirements detailed above.

Internal, related deaths and life-threatening events will be reported to the UCSF IRB and DSMB immediately.

8.3.7 REPORTING OF PREGNANCY

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

9 UNANTICIPATED PROBLEMS

9.1.1 DEFINITION OF UNANTICIPATED PROBLEMS

Per the UCSF Human Research Protection Program, we define unanticipated problems (also known as unexpected problems) as 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.

9.1.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the UCSF Institutional Review Board (IRB) and Data Safety Monitoring Board. 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, DSMB, 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, DSMB, 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, reviewed by the relevant medical monitor, and reviewed and signed off by the Principal Investigator.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Aim 1: Evaluate the efficacy of digital CBT-I for preventing perinatal depression. We hypothesize that participants randomized to digital CBT-I will have significantly lower rates of incident major depression during the perinatal period (**Hyp 1a**) and lower depressive symptoms from baseline to 12 months postpartum (**Hyp 1b**) relative to participants randomized to digital sleep hygiene education.

Aim 2: Test mediators of the effect of digital CBT-I on perinatal depression. We hypothesize that change in prenatal insomnia symptom severity will mediate the effect of digital CBT-I on perinatal depression incidence (**Hyp 2a**) and perinatal depressive symptom severity (**Hyp 2b**). Secondary mediators include perseverative negative thinking, dysfunctional beliefs about sleep, nocturnal cognitive arousal, and emotion regulation.

Aim 3: Test moderation of the effect of digital CBT-I on perinatal depression. We hypothesize that baseline depressive symptom severity will moderate the effect of digital CBT-I on perinatal depression incidence (**Hyp 3a**) and depressive symptom severity from baseline to 12 months postpartum (**Hyp 3b**).

10.2 SAMPLE SIZE DETERMINATION

Aim 1: Based on our preliminary data, we expect a 16% lower rate of depression among women in the digital CBT-I condition relative to women in the digital SHE condition. We conservatively power the study to detect a between-group difference of 10% in case the effect is smaller than expected. Standard power calculations for the comparison of two proportions show that with alpha set at 0.05, chi-square tests with 199 women per group would have power greater than 0.8 to detect this difference (**Hypothesis 1A**).[60]

The proposed sample size and number of repeated measures per woman are large enough to allow us to detect important differences in the magnitude of within-woman change in depressive symptom severity, measured by the EPDS, between the two conditions with high power (**Hypothesis 1B**). We will measure depression outcomes at 7 time points throughout the study period. The statistical analyses will compare within-subject changes in the EPDS over time between the two intervention conditions using linear mixed effects models. Sample size calculations for repeated measures studies require estimates of the magnitude of the within-subject correlation of the outcome; data from our previous trial of digital CBT-I provide us with an estimate of 0.5 for this correlation for the EPDS outcome.[8] Our previous trial also provides an estimate of 9.2 units for the within-subject variance of the EPDS measure. Standard power calculations for linear mixed effects models show that with an alpha set at the 0.05 level and with two conditions of 199 subjects each, we will have power greater than 80% to detect a difference in within-subject slopes of 0.04 (units of EPDS) per month between the two intervention groups.[61] In our previous trial, the estimated difference in slopes between digital CBT-I and standard care was 0.12.

Aim 2: We base sample size calculations on a statistical test to detect statistically significant mediation of the treatment effect on within-subject change in EPDS through within-subject change in ISI using linear regression. Standard sample size calculations for mediation using linear regression analysis require the specification of the variances of the depression outcome (EPDS), the treatment predictor, and the sleep mediator (ISI), the magnitude of the treatment effects without adjustment for the mediator, and the correlation of the mediator and treatment variables.[62] Data from our previous trial of digital CBT-I provide estimates for all of these quantities. Calculations[62] show that a standard test for mediation using our proposed sample will have power greater than 80% to detect a proportion of treatment effect explained (PTE) of 0.02. Using data from our previous trial of digital CBT-I for women and changes from baseline to 10 weeks, a linear regression with change in EPDS from baseline to 6 months postpartum as the outcome and treatment as the single predictor yielded an estimated regression coefficient of -0.14 (units of EPDS). Adding change in ISI to the model reduced the estimated treatment effect to -0.12 (units of EPDS), with an estimated PTE of 0.10, far exceeding 0.02.

Aim 3: We base sample size calculations on tests of the interaction of treatment condition with depressive symptoms at baseline (using established cutoff of EPDS < 10) in logistic regressions with incidence of probable major depression as the outcome. These sample size methods require the specification of several inputs that describe the anticipated prevalence of the outcome, predictors, and their relationships.[63] Calculations based on inputs from our previous digital CBT-I trial show that the proposed sample of 398 participants provide 80% power to detect an interaction odds ratio (ratio of odds ratio for baseline EPDS < 10 compared to baseline EPDS ≥ 10) of 4.1 with binary indicators for condition and depressive symptoms at baseline. Our previous trial yielded an estimated odds ratio of 10, indicating that the detectable interaction odds ratio of 4 is a realistic objective.

These calculations show that the proposed sample size will allow us to detect clinically important differences in depression incidence and changes in depressive symptom severity between women in the two intervention conditions, as well as clinically meaningful mediation and moderation effects, with 80% power. Based on our previous trial, we set our attrition rate at 20%, yielding a total enrolled sample size of 498.

10.3 POPULATIONS FOR ANALYSES

All analyses will be conducted on the intention-to-treat sample defined as all randomized participants. We will examine whether the depression prevention effect is dose dependent by including number of sessions completed as a covariate.

10.4 STATISTICAL ANALYSES

10.4.1 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.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Aim 1: To test *Hypothesis 1a*, we will compare the rate of major depression among women randomized to digital CBT-I to women randomized to digital SHE using a standard chi-square test for two proportions. The outcome is binary and indicates whether a participant experienced a depressive episode at any point since randomization (SCID-5). We will calculate a 95% confidence interval for the difference in the two proportions to quantify the magnitude of the CBT-I effect.

To test *Hypothesis 1b*, we will compare within-woman changes in depressive symptoms (EPDS; including data from baseline; 10-weeks post-randomization; 36 weeks gestation; 3, 6, 9, and 12 months postpartum) between women in the digital CBT-I and digital SHE groups using linear mixed effects models.[64] These models will include repeated measures of depressive symptoms as the outcome, along with time, treatment group, and time by group interactions as predictors. Models also will include random intercepts to accommodate the correlation among the repeated responses within subjects, and possibly random slopes to accommodate between subject differences in rates of change. The regression coefficient of the time by group interaction measures the differences in the rate of within-subject change in the outcomes between the treatment groups. We will calculate 95% confidence intervals for the time by group interaction to provide a range of differences in change that are consistent with the data. We will assess the statistical significance of the time by group interaction using likelihood ratio tests. We note that mixed effects models do not require the same number of repeated measures for each subject so that our approach will include all women who provide any data and will be an intention-to-treat approach. We will fit the mixed models using routines in Stata.

Although we expect that randomization will balance baseline characteristics (e.g., gestational age, parity, insomnia symptom severity) between the two conditions, we will calculate standardized mean differences to identify any imbalances. If we identify imbalances, we will conduct secondary analyses including imbalanced covariates as predictors. Additionally, we will conduct sensitivity analyses to examine whether findings change substantively when omitting participants with new onset of sleep, medical, or psychiatric disorders, or initiation of mental health treatment. Finally, we will examine whether the depression prevention effect of digital CBT-I is dose-dependent by including number of sessions completed as a covariate.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Aim 2: To test *Hypothesis 2a*, we will fit two logistic regression models to assess whether change in prenatal insomnia symptoms (ISI) mediates the effect of digital CBT-I on incidence of major depression from baseline to 12 months postpartum.[65] The first model will include the binary indicator of depression as the outcome and treatment group as the single predictor. The second model will additionally include subject-specific change in insomnia severity from baseline to 10-weeks post-randomization. We will estimate subject-specific changes in insomnia severity as the predicted random slopes from a linear mixed effects model with the repeated measures of insomnia severity as the outcome and time as the single predictor, along with random intercepts and time effects. Differences in the estimated treatment effects

between the two models indicate mediation by insomnia severity. We will assess whether the conditions for mediation are met by fitting two additional models: first, a linear regression model for subject-specific change in insomnia severity on treatment group; second, a logistic regression model for major depression on subject-specific change in insomnia severity. Statistically significant predictor effects in each of these models are consistent with mediation.

To test *Hypothesis 2b*, we will follow a similar approach to assess the potential mediation of the treatment effect on the changes in depressive symptoms (EPDS; including data from baseline; 10-weeks post-randomization; 36 weeks gestation; 3, 6, 9, and 12 months postpartum) by changes in prenatal insomnia severity (ISI) by fitting two linear mixed effects regression models. The first model is the linear mixed effects model for repeated measures of depressive symptoms we fit to test the hypothesis of Aim 1b, namely a model that includes treatment group, time, and the time by group interactions as the predictors, along with random intercepts and time effects. The second model will additionally include repeated measures of insomnia severity (ISI). We will decompose insomnia severity variable into between- and within-woman components in order to isolate pure within-woman change.[66] Differences in the estimated time by treatment interaction effects between the two models indicate mediation by changes in prenatal insomnia severity.

Aim 3: To test *Hypothesis 3a*, we will fit a logistic regression model with perinatal depression incidence as the outcome, along with treatment group, baseline depressive symptom severity, and their interaction as the predictors. The regression coefficient of the interaction term measures the difference in the effect of the digital CBT-I intervention as a function of level of baseline depressive symptom severity. We will test the statistical significance of the interaction using a likelihood ratio test and quantify the magnitude of the interaction effects using 95% confidence intervals for the interaction regression coefficient.

To test *Hypothesis 3b*, models will include repeated measures of depressive symptoms as the outcome, along with time, treatment group, and two-way interactions of depressive symptom severity with time and depressive symptom severity with treatment, as well as a three-way interaction of time, treatment, and depressive symptom severity. The three-way interaction term assesses whether the magnitude of the time by treatment group interaction (a primary treatment effect of Aim 1) differs as a function of baseline depression. We will assess the statistical significance of the three-way interaction using a likelihood ratio test and quantify the magnitude of the interaction effects using 95% confidence intervals for the interaction regression coefficient.

10.4.4 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.

10.4.5 PLANNED INTERIM ANALYSES

No planned interim analyses. The Data Safety Monitoring Board (DSMB) will review any serious adverse events to determine whether the trial should be stopped.

10.4.6 SUB-GROUP ANALYSES

We do not plan sub-group analyses.

10.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

10.4.8 EXPLORATORY ANALYSES

We will explore condition differences in gestational length, and explore potential mediators including perseverative negative thinking, dysfunctional beliefs about sleep, nocturnal arousal, and emotion regulation.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing the study intervention, study procedures, and risks will be given to the participant and documentation of electronic consent will be completed prior to starting the study intervention. 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.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Because this study involves no in-person visits, all consenting will occur electronically. There will be three consent forms: the screening consent, the future contact consent, and the study consent.

For all consents, potential participants will have the option to decline participation, consider their decision further, or consent to participate. Consent forms will be written at an eighth-grade education level, use lay language, and provide information about the background and purpose of the study, scope and length of participation, study procedures, 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. Potential participants 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. Potential participants 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.

Screening consent: First, potential participants will view an introduction page that briefly describes the study. Next, the screening consent form will be displayed and participants can choose to decline to agree to participate. Participants who decline will be automatically directed to the end of the survey and thanked for their time. Participants who agree will begin the screening survey.

Future contact consent: After completing the screening survey, regardless of eligibility, participants will be given the opportunity to input their contact information if they are interested in being contacted for future research studies at UCSF.

Study consent: The orientation session provides another opportunity to engage participants in the informed consent process. In this session, study staff will discuss the importance of the study question, the required commitments, what to expect if randomized to CBT-I or SHE, the rationale for random assignment, the consequences of attrition bias, and answer any questions that participants have.[29] Individuals who are interested in participating after the orientation session will be scheduled for a 1:1 appointment to complete the consenting process and the clinical interview to determine eligibility. Consenting participants will provide an electronic signature via REDCap.

Staff obtaining consent will receive training from Dr. Felder.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause as determined by the DSMB. The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy relevant regulatory or oversight bodies (e.g., DSMB, IRB, or NIMH).

If the study is prematurely terminated or temporarily suspended, the PI will promptly inform ongoing study participants, the IRB, and sponsor/funding agency and provide the reason(s) for the termination or temporary suspension.

11.1.3 CONFIDENTIALITY AND PRIVACY

Participants will be instructed to complete all research activities in a private setting.

Clinical interviews will be recorded for the purpose of assessing reliability. As is standard UCSF Zoom procedure, participants must agree before joining a recorded meeting. Any transcriptions of these recordings will not include information that links participant identity to the recording. All recordings will be destroyed 5 years after the project is complete, but researchers will retain de-identified transcripts of the recordings indefinitely.

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 participant identity to their unique coded identifier will be stored on REDCap. Access to all data will be limited to the PI and trained, authorized study staff. Below we provide a brief overview of how the programs and platforms used to collect data handle data confidentiality and security:

- REDCap (Participant tracking database; Online survey platform): Secure web application; HIPAA-compliant
- BigHealth (Sleepio; Digital CBT-I program): Dated stored in encrypted form on secure servers owned and operated by Amazon Web Services; HIPAA-compliant. We will sign a data use agreement form with BigHealth prior to data collection.
- Zoom: Provides encryption and meeting access controls (e.g., password) so data in transit cannot be intercepted; all audio, video, and screen sharing data is encrypted; Enables HIPAA-compliance.
- Qualtrics (Online survey platform): Certified by Health Information Trust Alliance, the industry standard for HIPAA security requirements; data encrypted in transit to protect from attacks, eavesdropping, and session hijacking; all data treated as highly confidential; physical security controls monitored 24/7

One limit to confidentiality is if a participant indicates during a clinical interview or on the EPDS or PHQ-9 that she is at imminent risk of harming herself. The procedures for responding to suicide risk are detailed in the Suicide Ideation Response Flow and C-SSRS Response Scripts.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

11.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of California, San Francisco. After the study is completed, the de-identified, archived data will be stored at the National Database for Clinical Trials related to Mental Illness (NDCT), for use by other researchers including those outside of the study. Permission to transmit data to the NDCT will be included in the informed consent.

11.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor (Psychiatric)**	**Medical Monitor (Medical)**
Jennifer Felder, PhD, Assistant Professor and Principal Investigator	Andrew Krystal, MD, Professor and Co-Investigator	Amanda Yeaton-Massey, MD, Assistant Professor and Co-Investigator
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11.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with appropriate expertise, including in perinatal mood and sleep, obstetrics and gynecology, and biostatistics. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least annually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be reviewed at the organizational meeting of the DSMB.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will undergo rigorous training prior to collecting or monitoring data. 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). Errors and their corrections will be logged in a data anomaly log. Clinical research coordinators will send reminders about interview appointments, and make multiple attempts to contact participants to complete follow-up measures.

Training and reliability of clinical interviewers. Training will be led by Dr. Manber, who has extensive experience training study staff to competently administer clinical interviews. Staff will complete an intensive 8- hour didactic and experiential training. For the didactic training, Dr.

Manber will review diagnostic criteria, orient staff to the interview questions, and discuss challenges for assessing sleep and psychopathology during the perinatal period. For the experiential training, staff will conduct role play interviews with self-critique and trainer feedback. After the intensive training, staff will rate training videos, and conduct and observe practice interviews with a confederate. Interviewers will need to establish interrater reliability > 0.8 with Dr. Manber before interviewing study participants. All interviews will be recorded. To prevent rater drift, Dr. Manber will lead quarterly reliability meetings during which staff will rate a randomly-selected interview. Dr. Manber will provide corrective feedback as needed and the team will discuss any variability in ratings. At study midpoint and endpoint, a random subset of 25% interviews will be selected to assess inter-rater reliability.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data will be collected directly from participants via electronic self-report questionnaires on REDCap and/or Qualtrics. Interview data will be entered directly into REDCap. Additionally, for participants randomized to digital CBT-I, BigHealth will provide information about number of sessions completed and sleep diary data.

11.1.8.2 STUDY RECORDS RETENTION

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

11.1.9 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, which may be on the part of the participant, the investigator, or the study site staff. We will follow the reporting requirements described by the UCSF IRB (*https://irb.ucsf.edu/protocol-violation-or-incident#Reporting-requirements-chart*).

11.1.10 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 trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.
- Every attempt will be made to publish results in peer-reviewed journals.

- We will share de-identified data with the research community via the National Database for Clinical Trials related to Mental Illness (NDCT).

11.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11.2 ABBREVIATIONS AND SPECIAL TERMS

ADM	Antidepressant Medication
AE	adverse events
BISQ-R	Brief Infant Sleep Questionnaire – Revised
C-SSRS	Columbia Suicide Severity Rating Scale
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTSA	Clinical and Translational Awards
DBAS	Dysfunctional Beliefs About Sleep scale
DERS-SF	Difficulties in Emotion Regulation Scale-Short Form
DSMB	Data Safety and Monitoring Board
EPDS	Edinburgh Postnatal Depression Scale
GAD-7	Generalized Anxiety Disorder Scale
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
Hyp	hypothesis
IBQ-R	Infant Behavior Questionnaire – Revised
ICH GCP	International Council on Harmonisation Good Clinical Practice
iOS	iPhone Operating System
IRB	International Review Board
ISI	Insomnia Severity Index
MPAS	Maternal Postnatal Attachment Scale

NCT	National Clinical Trial
NDCT	National Database for Clinical Trials
NIH	National Institutes of Health
NIHGPS	National Institutes of Health Grants Policy Statement
PDF	Portable Document Format
PHQ-9	Patient Health Questionnaire
PI	Primary Investigator
PRP	Participant Recruitment Program
PSAS	Pre-sleep Arousal Scale
PSQI	Pittsburgh Sleep Quality Index
PTBi CAB	Preterm Birth Initiative Community Advisory Board
PTE	proportion of treatment effect
PTQ	Perseverative Thinking Questionnaire
RCT	Randomized Control Trial
SOA	Schedule of Activities
RLS	Restless Leg Syndrome
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-5 Disorders
SCISD	Structured Clinical Interview for DSM-5 Sleep Disorders
SHE	sleep hygiene education
UCSF	University of California San Francisco
UPs	unanticipated problems
US	United States

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

12 REFERENCES

1. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: A systematic review of prevalence and incidence. *Obstetrics and Gynecology.* 2005;106(5):1071-1083.
2. Khalifeh H, Hunt IM, Appleby L, Howard LM. Suicide in perinatal and non-perinatal women in contact with psychiatric services: 15 year findings from a UK national inquiry. *Lancet Psychiatry.* 2016;3(3):233-242.
3. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. *Lancet.* 2014;384(9956):1800-1819.
4. Luca DL, Garlow N, Staatz C, Margiotta C, Zivin K. *Societal costs of untreated perinatal mood and anxiety disorders in the United States.* 2019.
5. Felder JN, Laraia B, Coleman-Phox K, et al. Poor sleep quality, psychological distress, and the buffering effect of mindfulness training during pregnancy. *Behav Sleep Med.* 2018;16(6):611-624.
6. Tomfohr LM, Buliga E, Letourneau NL, Campbell TS, Giesbrecht GF. Trajectories of sleep quality and associations with mood during the perinatal period. *Sleep.* 2015;38(8):1237-1245.
7. Suri R, Stowe ZN, Cohen LS, et al. Prospective longitudinal study of predictors of postpartum-onset depression in women with a history of major depressive disorder. *Journal of Clinical Psychiatry.* 2017;78(8):1110-1116.
8. Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. Efficacy of digital cognitive behavioral therapy for the treatment of insomnia symptoms among pregnant women: A randomized clinical trial. *JAMA Psychiatry.* 2020.
9. Thomas A, Grandner M, Nowakowski S, Nesom G, Corbitt C, Perlis ML. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. *Behav Sleep Med.* 2016;14(6):687-698.
10. Flynn HA, Henshaw E, O'Mahen H, Forman J. Patient perspectives on improving the depression referral processes in obstetrics settings: A qualitative study. *General Hospital Psychiatry.* 2010;32(1):9-16.
11. Espie CA, Emsley R, Kyle SD, et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: A randomized clinical trial. *JAMA Psychiatry.* 2019;76(1):21-30.
12. Espie CA, Kyle SD, Williams C, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep.* 2012;35(6):769-781.
13. Carney CE, Edinger JD, Kuchibhatla M, et al. Cognitive behavioral insomnia therapy for those with insomnia and depression: A randomized controlled clinical trial. *Sleep.* 2017;40(4).
14. Gelaye B, Addae G, Neway B, et al. Poor sleep quality, antepartum depression and suicidal ideation among pregnant women. *J Affect Disord.* 2017;209:195-200.
15. Osnes RS, Roaldset JO, Follestad T, Eberhard-Gran M. Insomnia late in pregnancy is associated with perinatal anxiety: A longitudinal cohort study. *Journal of Affective Disorders.* 2019;248:155-165.

16. Furtado M, Van Lieshout RJ, Van Ameringen M, Green SM, Frey BN. Biological and psychosocial predictors of anxiety worsening in the postpartum period: A longitudinal study. *J Affect Disorders.* 2019;250:218-225.
17. Moss TG, Lachowski AM, Carney CE. What all treatment providers should know about sleep hygiene recommendations. *The Behavior Therapist.* 2013;36(4):76-83.
18. Felder JN, Hartman AR, Epel ES, Prather AA. Pregnant patient perceptions of provider detection and treatment of Insomnia. *Behav Sleep Med.* 2019:1-10.
19. Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. Randomized controlled trial of digital cognitive behavior therapy for prenatal insomnia symptoms: Effects on postpartum insomnia and mental health. *Sleep.* 2021.
20. Prendeville W. Epidemiology of miscarriage. In: Grudzinskas JG, O'Brien PMS, eds. *Problems in early pregnancy: advances in diagnosis and management*: RCOG Press; 1997.
21. Pew Research Center. Mobile technology and home broadband 2019. June 2019.
22. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* 2011;34(5):601-608.
23. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125-133.
24. Taylor DJ, Wilkerson AK, Pruiksma KE, et al. Reliability of the Structured Clinical Interview for DSM-5 Sleep Disorders Module. *J Clin Sleep Med.* 2018;14(3):459-464.
25. First MB, Williams JbW, Karg RS, Spitzer RL. *Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV).* Arlington, VA: American Psychiatric Association; 2015.
26. Facco FL, Ouyang DW, Zee PC, Grobman WA. Development of a pregnancy-specific screening tool for sleep apnea. *J Clin Sleep Med.* 2012;8(4):389-394.
27. Vignato J, Landau E, Duffecy J, O'Hara MW, Segre LS. Using mobile health applications for the rapid recruitment of perinatal women. *Archives of Womens Mental Health.* 2019;22(2):305-308.
28. Manber R, Bei B, Simpson N, et al. Cognitive behavioral therapy for prenatal insomnia: A randomized controlled trial. *Obstet Gynecol.* 2019;133(5):911-919.
29. Goldberg JH, Kiernan M. Innovative techniques to address retention in a behavioral weight-loss trial. *Health Educ Res.* 2005;20(4):439-447.
30. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297-307.
31. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep.* 2012;35(2):287-302.
32. Maich KHG, Lachowski AM, Carney CE. Psychometric properties of the Consensus Sleep Diary in those with insomnia disorder. *Behav Sleep Med.* 2018;16(2):117-134.
33. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-1277.

34. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry.* 1987;150:782-786.
35. Matthey S, Henshaw C, Elliott S, Barnett B. Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale: Implications for clinical and research practice. *Archives of Womens Mental Health.* 2006;9(6):309-315.
36. Murray D, Cox JL. Screening for depression during pregnancy with the Edinburgh Depression Scale (EPDS). *Journal of Reproductive and Infant Psychology.* 1990;8:99-107.
37. Kozinszky Z, Dudas RB. Validation studies of the Edinburgh Postnatal Depression Scale for the antenatal period. *J Affect Disord.* 2015;176:95-105.
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.
39. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med.* 2006;166(10):1092-1097.
40. Simpson W, Glazer M, Michalski N, Steiner M, Frey BN. Comparative efficacy of the Generalized Anxiety Disorder 7-Item Scale and the Edinburgh Postnatal Depression Scale as screening tools for generalized anxiety disorder in pregnancy and the postpartum period. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie.* 2014;59(8):434-440.
41. Baer RJ, Chambers CD, Bandoli G, Jelliffe-Pawlowski LL. Risk of preterm birth by subtype among Medi-Cal participants with mental illness. *Am J Obstet Gynecol.* 2016;215(4):e1-9.
42. Felder JN, Baer RJ, Rand L, Jelliffe-Pawlowski LL, Prather AA. Sleep disorder diagnosis during pregnancy and risk of preterm birth. *Obstet Gynecol.* 2017;130(3):573-581.
43. Bat-Erdene U, Metcalfe A, McDonald SW, Tough SC. Validation of Canadian mothers' recall of events in labour and delivery with electronic health records. *BMC pregnancy and childbirth.* 2013;13 Suppl 1:S3.
44. Gresham E, Forder P, Chojenta CL, Byles JE, Loxton DJ, Hure AJ. Agreement between self-reported perinatal outcomes and administrative data in New South Wales, Australia. *BMC Pregnancy and Childbirth.* 2015;15(161).
45. Ehring T, Zetsche U, Weidacker K, Wahl K, Schönfeld S, Ehlers A. The Perseverative Thinking Questionnaire (PTQ): Validation of a content-independent measure of repetitive negative thinking. *Journal of behavior therapy and experimental psychiatry.* 2011;42(2):225-232.
46. Cheng P, Kalmbach DA, Castelan AC, Murugan N, Drake CL. Depression prevention in digital cognitive behavioral therapy for insomnia: Is rumination a mediator? *J Affect Disord.* 2020;273:434-441.
47. Kalmbach DA, Cheng P, Roth T, et al. Examining Patient Feedback and the Role of Cognitive Arousal in Treatment Non-response to Digital Cognitive-behavioral Therapy for Insomnia during Pregnancy. *Behavioral Sleep Medicine.* 2021:1-20.
48. Mitchell AM, Christian LM. Repetitive negative thinking, meaning in life, and serum cytokine levels in pregnant women: Varying associations by socioeconomic status. *Journal of behavioral medicine.* 2019;42(5):960-972.

49. Schmidt D, Seehagen S, Hirschfeld G, Vocks S, Schneider S, Teismann T. Repetitive negative thinking and impaired mother–infant bonding: A longitudinal study. *Cognitive Therapy and Research.* 2017;41(3):498-507.
50. Morin CM, Vallières A, Ivers H. Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). *Sleep.* 2007;30(11):1547-1554.
51. Norell-Clarke A, Tillfors M, Jansson-Fröjmark M, Holländare F, Engström I. How does cognitive behavioral therapy for insomnia work? An investigation of cognitive processes and time in bed as outcomes and mediators in a sample with insomnia and depressive symptomatology. *International Journal of Cognitive Therapy.* 2017;10(4):304-329.
52. Nicassio PM, Mendlowitz DR, Fussell JJ, Petras L. The phenomenology of the pre-sleep state: the development of the pre-sleep arousal scale. *Behaviour research and therapy.* 1985;23(3):263-271.
53. Kalmbach DA, Cheng P, Drake CL. A pathogenic cycle between insomnia and cognitive arousal fuels perinatal depression: exploring the roles of nocturnal cognitive arousal and perinatal-focused rumination. *Sleep.* 2021.
54. Kaufman EA, Xia MY, Fosco G, Yaptangco M, Skidmore CR, Crowell SE. The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): Validation and replication in adolescent and adult samples. *Journal of Psychopathology and Behavioral Assessment.* 2016;38(3):443-455.
55. Predatu R, Voinescu BI, David DO. The Role of Emotion Regulation Difficulties in the Relation Between Insomnia and Depressive Symptoms. *International Journal of Behavioral Medicine.* 2020;27(6):615-622.
56. Hallion LS, Steinman SA, Tolin DF, Diefenbach GJ. Psychometric properties of the Difficulties in Emotion Regulation Scale (DERS) and its short forms in adults with emotional disorders. *Frontiers in Psychology.* 2018;9(539).
57. Cheng P, Kalmbach DA, Tallent G, Joseph CL, Espie CA, Drake CL. Depression prevention via digital cognitive behavioral therapy for insomnia: A randomized controlled trial. *Sleep.* 2019;42(10).
58. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry.* 2000;31(2):73-86.
59. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: Development of a general scale. *Evaluation and Program Planning.* 1979;2:197-207.
60. Cohen J. *Statistical power analysis for the behavior sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
61. Diggle PJ, Heagerty PJ, Liang K-Y, Zeger SL. *Analysis of longitudinal data, Second edition.* Oxford: Oxford University Press; 2002.
62. Vittinghoff E, Sen S, McCulloch CE. Sample size calculations for evaluating mediation. *Stat Med.* 2009;28(4):541-557.
63. Demidenko E. Sample size and optimal design for logistic regression with binary interaction. *Stat Med.* 2008;27(1):36-46.
64. McCulloch CE, Searle SR, Neuhaus JM. *Generalized, Linear, and Mixed Models, Second Edition.* New York: Wiley; 2008.
65. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. *Regression Models in Biostatistics, Second Edition.* New York: Springer; 2012.

66. Neuhaus JM, McCulloch CE. Separating between- and within-cluster covariate effects by using conditional and partitioning methods. *Journal of the Royal Statistical Society Series B-Statistical Methodology.* 2006;68:859-872.