

A Wearable Morning Light Treatment for Postpartum Depression

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A WEARABLE MORNING LIGHT TREATMENT FOR POSTPARTUM DEPRESSION

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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 Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as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 form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

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

Principal Investigator:

Signed:



Date: 11/16/2020

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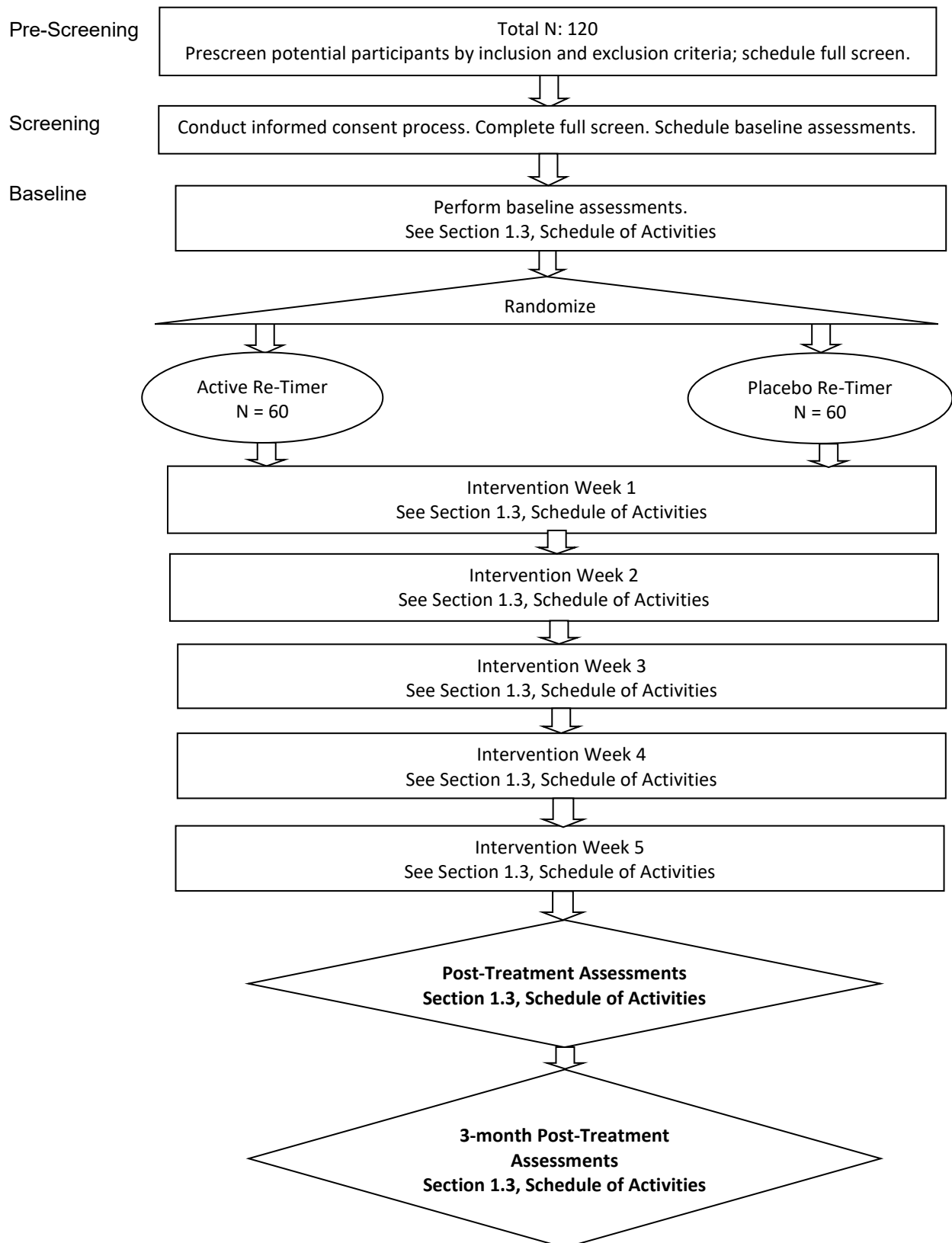
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Wearable Morning Light Treatment for Postpartum Depression
Grant Number:	R01MH121531 - 01A1
Study Description:	The proposed study is a double-blind, randomized placebo-controlled study of Re-Timer® wearable morning bright light therapy relative to wearable dim light placebo for postpartum depression. The objectives of the study are to establish the effect of wearable morning bright light on postpartum depression symptoms, changes in phase angle difference (relationship between sleep and circadian timing), and functioning in women with postpartum depression. We propose to enroll 120 women who are within 6 months postpartum and meet diagnostic criteria for an episode of major depressive disorder.
Objectives:	Primary Objectives: 1. Establish the effect of wearable morning bright light therapy vs. dim light placebo on clinician-rated postpartum depression symptoms. 2. Establish changes in the phase angle difference (PAD) as a predictor of improvement in postpartum depression. Secondary Objectives: Test the effect of morning bright light therapy on secondary outcomes (phase angle difference, self-reported depression and maternal functioning).
Endpoints:	Primary Endpoints: Hamilton Rating Scale for Depression-17 item version (HAMD 17-item) total score; Secondary Endpoints: Phase Angle Difference, total score on the following measures: Edinburgh Postnatal Depression Scale; Epworth Sleepiness Scale; Satisfaction with Participation in Social Roles; Sleep-Related Impairment; Parental Bonding Questionnaire; Hamilton Rating Scale for Depression, Seasonal Affective Disorders Version (SIGH-SAD, 29 items)
Study Population:	120 women who are within 6 months postpartum and meet diagnostic criteria for major depression disorder
Description of Study Intervention/Experimental Manipulation:	Light administered via Re-Timer® light therapy glasses, worn in the morning for 60 minutes daily for 5 weeks. Participants are assigned to active intervention (bright light Re-Timer®) or placebo (dim light Re-Timer®).
Study Duration:	Approximately 48 months
Participant Duration:	Approximately 3-4 months

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

Time Point	Screening /Clinician Ratings Baseline	Baseline (Self- report)	Week 1	Week 2	Week 3	Week 4	Week 5/ Post-Tx	3-Mos Post-Tx
Study Day		-7 to 0 ± 7	1 to 7 ± 7	7 to 14 ± 7	14 to 21 ± 7	21 to 28 ± 7	28 to 35 ± 7	125 ± 14
Study Activities								
Screening (SCID, STOP-BANG, RLS questionnaire, clinical/medical history)								
Randomization								
Re-Timer Intervention (Active or Placebo)								
Tx Adherence Check								
Adverse Events Reporting								
Study Assessments								
Dim Light Melatonin Onset Collection (saliva); 1 day/timepoint								
Light Tx Log								
Maternal Actigraphy and Sleep Diary (4-7 days/timepoint)								
Infant Actigraphy (approx. 4-5 days/ timepoint)								
Medications List								
Hamilton Rating Scale for Depression (Seasonal Affective Disorders Version, SIGH-SAD)								
Edinburgh Postnatal Depression Scale (EPDS)								
Epworth Sleepiness Scale (ESS)								
Sleep-Related Impairment (SRI)								
Participation in Social Roles (SPSR)								
Postpartum Bonding Questionnaire (PBQ)								
Morningness-Eveningness Questionnaire (MEQ)								
Columbia Suicide Severity Rating Scale (CSSRS)								
Treatment Expectation/Evaluation								
Dietary Screener Questionnaire								
Eating Habits Questionnaire								
Side Effects								
Tx = Treatment								

2 INTRODUCTION

2.1 STUDY RATIONALE

As one of the most common pregnancy complications, nearly 600,000 women in the United States suffer from postpartum depression annually. Consequences of postpartum depression are far-reaching and include maternal suicide, functional impairment, and impaired development and psychiatric illness in offspring. Despite the high prevalence and significant consequences, under current treatment paradigms less than 16% of women with postpartum depression receive treatment and only 3.2% in total achieve remission. Treatment uptake in this population is influenced by concerns regarding pharmacotherapy during lactation and caregiving demands for a newborn. Novel treatments that remove the significant obstacles to accessing care inherent to the postpartum period, such as non-pharmacological therapies delivered in-home, are urgently needed. Morning bright light therapy advances circadian timing and is an effective antidepressant for seasonal and non-seasonal depression. Importantly, bright light therapy is a non-pharmacological intervention that is administered in-home. However, its efficacy in postpartum depression, and mechanism of action, have not been confirmed. Further, traditional light therapy delivered via light box has limited utility for postpartum women, as the user must remain stationary during the treatment and it may expose the infant to light. Through recent technological innovations, wearable bright light therapy devices (i.e., Re-Timer®) are now available; advantages for postpartum women include freedom of movement during treatment and targeted light exposure limited to the user's ocular area, so infants are not exposed to the light.

2.2 BACKGROUND

One of the most common pregnancy complications, postpartum depression (PPD) affects up to 20% of women [1]. Highly recurrent [2], PPD can precipitate suicide, a leading cause of postpartum death [3]. Maternal functioning, including bonding with the infant, is impaired by PPD, with serious consequences for offspring [4]. Rates of PPD treatment are alarmingly low: less than 16% of cases are treated, only 6.2% receive adequate treatment, and 3.2% achieve remission under current treatment paradigms [5]. Treatment barriers include pharmacotherapy concerns and the burden of clinic-based treatments (e.g., travel, childcare [6]). Novel, non-pharmacological treatment approaches are critical to improve outcomes for women and offspring.

Circadian rhythms are a promising, yet understudied, PPD intervention target. The postpartum period is rife with factors that contribute to circadian misalignment (i.e., divergence between the circadian timing and sleep-wake systems). Estrogen and progesterone, modulators of the circadian system, fluctuate substantially in early postpartum [7]. Caring for an infant may misalign the circadian timing and sleep-wake systems through sleep-wake variability; napping; exposure to light at night; and insufficient exposure to daytime light [8, 9]. A circadian phase delay (clock shifts later) is associated with PPD symptoms [10] and seen in women with PPD relative to healthy postpartum controls [11].

As a robust chronobiotic, morning bright light therapy advances circadian timing (shifts clock earlier) [12]. Effective for depression in non-perinatal populations [13], morning bright light therapy remains relatively unstudied in PPD. As an in-home, non-pharmacological intervention with rapid treatment effects and few side effects, morning bright light therapy holds many advantages for the treatment of PPD. However, the traditionally used light box has limited utility for postpartum women, as it requires the user to remain stationary and may expose the infant to bright light. Novel light therapy interfaces, such as wearable light therapy glasses, would address such barriers, but have not been tested in the postpartum population.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1. Risk of violation of confidentiality of assessment data

The risk of violation of confidentiality exists because human participants are giving personal information during assessments. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., psychiatric symptoms). Note that confidentiality may be breached to protect the subject or others if there is evidence of imminent danger to the subject or others (i.e., deemed to be at high risk for suicide or homicide, evidence of child abuse/neglect). This limit to confidentiality is explicitly stated in the consent form. In such situations, we will use procedures identical to those in place at the University of Michigan (UM) Department of Psychiatry if child abuse or neglect is suspected. Briefly, first we will make an anonymous call to the UM Child Protection Team, and describe the situation as fully as possible and obtain advice as to whether the situation requires reporting to Child Protective Services (CPS). If so, a report will be made and CPS will provide intervention from that point. If a report is not warranted, the study investigators will be consulted to determine whether further assessment of child safety and well-being is necessary. If any risk to a child is suspected and CPS dictates that they need not be involved, the study team will consult with the subject to negotiate a safety plan for the child/ren, which will require the involvement of significant others as deemed safe and appropriate by the study team and subject. Any needed additional support and services will be provided to the subject. All of these issues will be closely monitored by the study team. All procedures will be documented.

2. Risk of psychological discomfort during assessments

There is a slight risk of psychological discomfort to study participants from the questions asked in the assessments. Participants may become anxious or uncomfortable as a result of being asked personal questions. The study team members conducting assessments are trained to respond to this emotional distress and to refer the participant to their mental health provider or other appropriate resources, as necessary. All participants are free to terminate the assessments at any time or refuse to respond to any questionnaire item.

3. Risks from saliva collection

There is a very slight risk of choking on the salivette collection swab. Participants will be shown appropriate collection techniques and this risk is very rare.

4. Risks from actigraphy

There is a very slight risk of minor skin irritation due to wearing of the actigraph.

5. Side effects from the use of morning bright light therapy

Morning light treatment is considered safer than sunlight because there are no UV rays, and indeed no changes in extensive ophthalmologic examination were observed after up to 6 years of daily light treatment (in fall and winter) [14]. The most common side effects of morning bright light therapy include headache, eyestrain or eye irritation, nausea, agitation/irritability, but these side effects often spontaneously remit [15, 16]. A rare but serious side effect is mania in patients with bipolar disorder who overexpose themselves to the light [15, 16], but individuals with bipolar disorder are excluded from this study and all participants will be provided with strict instructions to limit their light treatment to 1 hour/day. Note that mania in response to morning light treatment is so rare that light treatment has even been clinically tested in bipolar patients and found to be safe [17]. Additionally, the Re-Timer® automatically

turns off after 1 hour of use. The circadian phase shifts (~1-2 hours) resulting from the active morning light treatment may lead to transient symptoms akin to jet lag after crossing 1-2 time zones, including transient sleepiness, fatigue and headache. These symptoms are similar to those experienced on a Monday morning after a late weekend. However, such 'jet lag' symptoms are expected to be short lived.

Light from the Re-Timer® is UV-free, the device has been independently tested for eye safety to the international standard CEI IEC 62471 and has been successfully used in other trials. Further, all participants will be instructed to not permit family/friends to play with the Re-Timer®, and to only turn the Re-Timer® on during the scheduled time. The bright light treatment will result in light intensities greater than most indoor light, but much dimmer than sunlight on a bright day (about 100,000 lux). The Re-Timer® is commercially available and already in use in the general population. The Re-Timer® meets international ultraviolet and blue light hazard safety standards (standard ICNIRP 7/99 and CIE S009/E: 2002, also known as international standard IEC 62471/Ed. 1 published in 2006), and is safe (no UV light, no power in wavelengths <400nm).

6. Risk of worsening mental or emotional state

As in any depression treatment trial, there is a risk of worsening mental or emotional state. Some participants may show a worsening of psychological symptoms or suicidality during the course of the study period, regardless of assigned treatment arm. Among individuals for depression, it is common for symptoms of emotional distress, including depression, hopelessness, and suicidal ideation to wax and wane. Thus, this risk is inherent in the population. We do not believe these risks are increased as a function of being enrolled in this study; if anything, we expect these symptoms to decrease as a function of being in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

Study participants may not directly benefit from participating in this study. Postpartum depression is common, undertreated, and has far reaching consequences for both mother and child. Novel, in-home treatments that remove barriers to care and target modifiable underpinnings are urgently needed. This study will test the efficacy of wearable bright light therapy for postpartum depression and determine how changes in sleep and circadian timing influence treatment response. The risk to participants is minimal. Participants have the option of dropping out of the study at any time. Participants may experience improvements in their depressive symptoms and functioning as a result of their use of the Re-Timer during this study. The potential benefit to others is that the study may advance our understanding of how morning light therapy may lead to therapeutic benefit for postpartum depression. Given that the potential risks associated with participating are minor and the potential benefits are considerable, it is believed that the risks are greatly outweighed by the benefits.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Protections Against Risk

Confidentiality of data

Multiple steps are taken to ensure the confidentiality of sensitive information. The study team has considerable experience in maintaining the confidentiality of participant data and has established procedures to ensure data confidentiality. First, every effort is made to ensure that all study data are always confidential, in terms of staff training and data storage, so that data cannot be linked to a particular person. The study coordinator, RA's, and clinicians will sign a pledge of confidentiality and will understand that violation of confidentiality is reason for dismissal. Training of staff will include information

about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants. All investigators and research staff will be required to fulfill all training requirements for Good Clinical Practice (GCP) and for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA). Subjects are reminded that they do not have to answer questions that make them feel uncomfortable, which reinforces the voluntary nature of their participation. The confidentiality of all information gathered directly from subjects or obtained from the patient's medical records is assured by assigning records a coded research number and identifying all computer and paper files only by this code. A single tracking file will link the codes with subject identifiers, such as name, contact information, and/or medical record number. In addition, consent forms and payment forms will be saved electronically on a secure platform. All files will be kept in locked file drawers in locked rooms, to which only authorized research personnel have access. Electronic records will be kept on secure servers, and records with identifying information will be kept separate from records used to collect research data. Only staff members who have a need-to-know personal identifying information will have access to this information. Screening data for subjects who do not qualify for the study will be destroyed, except for anonymous information unlinkable to the subjects (such as age, gender and education). After the completion of data analysis, the record linking subjects to the research codes will be destroyed, thereby anonymizing the data.

All data will be collected electronically using REDCap, a secure HIPAA-compliant web application that facilitates the collection and entry of research data. Any paper forms containing research data will be stored in locked file cabinets in the study coordinator's office. Computer data files will be saved with passwords. Any paper copies of consent forms will be stored separately from data in locked cabinets, because they contain identifying information/ participant ID. The identifiers will be maintained as long as data collection activities are ongoing, and up to 7 years following the completion of the study. At the study's conclusion, the electronic file linking study IDs with patient identifiers will be destroyed. Reporting of the research will involve aggregate data which will not permit identification of any individual patients.

Risks of psychological discomfort

Completion of self-report and clinician-rated measures regarding sleep and mood may cause some emotional discomfort in participants or may find some of the questions uncomfortable to answer. In order to minimize these risks all interviews will be conducted by trained research staff. Participants are informed that they are free to take a break during interviews. The informed consent document clearly states that participants are free to refuse to answer any and all questions or end the interview at any time. Participants are reminded at the outset of interviews that they are free to withdraw at any time or refuse to answer questions. Research staff are trained to be sensitive to signs of participant distress and to suggest breaks when appropriate.

Risk of choking on the salivette

There is a very slight risk of choking on the salivette when taking saliva samples. These risks will be minimized by proper training on the technique by a member of the study team and instructions delivered with the DLMO kits.

Risk of minor skin irritation from the actigraph

Slight risks involved with wearable devices such as actigraphs include risk of skin irritation. To minimize these risks participants will be advised to keep the band clean, dry, and appropriately tightened. If irritation persists, they are advised to cease wearing the device and to notify members of the study team.

Risks involved with use of the Re-Timer® morning bright light therapy

Bright light devices are safe, with no changes in extensive ophthalmologic examination observed after up to 6 years of daily use (in fall and winter months) [14]. The Re-Timer® used in this study is commercially available and already in use in the general population. The Re-Timer® meets international ultraviolet and blue light hazard safety standards (standard ICNIRP 7/99 and CIE S009/E: 2002, also known as international standard IEC 62471/Ed. 1 published in 2006), and is safe (no UV light, no power in wavelengths <400nm). Light treatment is associated with some side effects, the most common being headache, eyestrain, nausea and agitation [15], and these and unanticipated symptoms will be monitored weekly during the light treatments. To aid in this monitoring, participants will complete the SAFTEE symptom checklist (modified to including only symptom domains relevant to light therapy) weekly through the treatment interval, consistent with other light treatment trials [17]. If a participant reports significant worsening in any of these symptoms from baseline (i.e., an increase in 2 points or more from baseline and score is “4” bothered quite a bit or “5” bothered extremely, or endorses the “trigger points” detailed below), Dr. Swanson or the study coordinator will contact the participant for more information and refer the matter to Dr. Muzik as needed (Co-I). Dr. Muzik will contact the participant as deemed necessary for more information. Dr. Muzik may decide to withdraw the participant from the trial and refer them for appropriate treatment. Again, participants will also be informed that if they experience any unexpected or significant deleterious changes in their condition, then they should immediately contact Dr. Swanson (unblinded) and/or the study coordinator. Dr. Swanson will then contact Drs. Muzik and Burgess as required.

Trigger items on the SAFTEE (if they represent any increase from baseline):

- loss of consciousness (2 or more)
- seizures (2 or more)
- chest pain (2 or more)
- shortness of breath (2 or more)
- rapid heart rate (2 or more)
- irregular heart beat (2 or more)
- feeling restless or like you cannot stay still (3 or more)
- too much energy or feeling wired (3 or more)
- jumpiness or feeling jittery (3 or more)
- feeling excited, overactive, or elated (3 or more)

Clinical deterioration and suicide risk:

Worsening of depressive symptoms or suicide is a possible risk for any study that enrolls individuals with depression. The comprehensive written informed consent documents for the study will outline potential limits of confidentiality based on suicide risk. Participants are provided with a handout summarizing warning signs of worsening mood, and circumstances under which they should contact the study investigators to notify us of worsening depression, and circumstances under which they should seek emergency services. All participants are administered the Columbia Suicide Severity Rating Scale (C-SSRS [18]) at the eligibility screen, and weekly through treatment. Participants deemed to be acutely suicidal, or at high risk for suicide at the eligibility screen per C-SSRS guidelines (i.e., presence of any suicidal behavior—suicide attempt, interrupted attempt, aborted attempt, or preparatory behavior—in the past 3 months; and/or current active suicidal ideation with any intent), or as determined by the principal investigator, will not be enrolled in the study.

Depressive symptoms and risk for suicide will be assessed at each study assessment. Two study team members are licensed mental health professionals, both with extensive experience in perinatal depression: Dr. Swanson is a licensed clinical psychologist; Dr. Muzik is a licensed psychiatrist. Any

worsening of ≥ 12 points from baseline or a previous assessment on the SIGH-SAD clinician-rated depression measure will be flagged for review by Dr. Swanson. A trend (i.e., at least 2 consecutive assessments) of worsening of ≥ 12 points is grounds for discontinuing the participant to clinical care, with careful follow up until clinical care is established. The study team may also refer subjects who do not meet these criteria for additional depression treatment as they deem necessary. Referral for appropriate clinical care will be initiated as necessary and participants will receive close follow-up from the study team during the transition to clinical care. Drs. Swanson and Muzik are very experienced in treatment of perinatal depression in both clinical and research settings. Patients who are local to the Ann Arbor area are referred to the Women's Mental Health and Infants Clinic at the University of Michigan. Dr. Muzik is the medical director of this clinic and can facilitate referral. If they live outside the Ann Arbor area, they are referred to appropriate clinics in their area.

If a participant is determined to be at risk for suicide, several steps will be followed: (1) ongoing contact with the participant will occur until risk is determined to be minimal; (2) all of the investigators will be informed immediately and continuously apprised of any changes/developments in the participant's risk for suicide; (3) all assessments, conversations, and steps taken with the participant to ensure her safety will be thoroughly documented. Participants at risk for suicide may be referred for clinical care as described above as necessary.

Suicide risk categories outlined below were developed using clinical guidelines for the C-SSRS, which will be administered during the study eligibility screen and weekly through treatment. The specific protocol to be followed for responding to suicide risk is as follows:

(1) Mild Risk (e.g., suicidal ideation present without presence of current plan, low intent, presence of hope, no current method; positive answers to questions 1 or 2 on C-SSRS suicidal ideation scale with negative answers to questions 3-5): The individual will be encouraged to call the UMHS Psychiatric Emergency Service (PES). She will also be encouraged to discuss her feelings with family members. Should family members be present at the time of interview/intervention, their immediate involvement will be enlisted. Follow-up contact by the mental health professionals on the research team (Drs. Swanson and Muzik) will be provided until risk is determined to be minimal.

(2) Moderate risk (e.g., suicidal ideation present with additional risk factors: moderate intent, low hope, possible plan and/or possible means; positive answers to question 3 on C-SSRS with negative answers to questions 4 and 5): The individual will be encouraged to contact the UM Psychiatric Emergency Service (PES), which operates 24 hours per day, 7 days per week, or her local Emergency Department if she resides outside the Ann Arbor area. If she refuses to contact PES or her local Emergency Department, we will enlist the assistance of a family member in doing so. If she refuses to enlist family, or family members are not present, she will be encouraged to have the clinician contact PES or her local Emergency Department for her. Should she refuse, and if no one is in the home to ensure her ongoing safety, the clinician will make the phone call against her will. Continuous follow-up phone call contact ensuring the participant's safety will occur throughout the day and then on a daily basis until risk is determined to be minimal. The patient will be told at the outset of participation that if suicide risk is present and they cannot be reached by phone, the local safety authorities or police will be contacted.

(3) High risk (e.g., suicidal ideation present with several additional risk factors: high intent, no hope, a definite plan, and current means; positive answers to questions 4 or 5 on C-SSRS): The individual will be encouraged to contact the UM Psychiatric Emergency Service (PES) or her local Emergency Department if she resides outside the Ann Arbor area. If she refuses to contact PES or her local

Emergency Department, we will enlist the assistance of a family member in doing so. If she refuses to enlist family, or family members are not present, she will be encouraged to have the clinician contact PES or her local Emergency Department for her. Should she refuse, and if no one is in the home to ensure her ongoing safety, the clinician will make the phone call against her will. The PES or local Emergency Department will send a unit or the police to the home. The clinician will remain in constant telephone contact until the participant's safety is ensured. Should the participant refuse hospitalization and it is deemed necessary, the clinician will engage police and authorities in ensuring involuntary hospitalization. Ongoing follow-up will occur until risk is determined to be minimal.

Potential Benefits of the Proposed Research to Research Participants and Others

Study participants may not directly benefit from participating in this study. Postpartum depression is common, undertreated, and has far reaching consequences for both mother and child. Novel, in-home treatments that remove barriers to care and target modifiable underpinnings are urgently needed. This study will test the efficacy of wearable bright light therapy for postpartum depression and determine how changes in sleep and circadian timing influence treatment response. The risk to participants is minimal. Participants have the option of dropping out of the study at any time. Participants may experience improvements in their depressive symptoms and functioning as a result of their use of the Re-Timer during this study. The potential benefit to others is that the study may advance our understanding of how morning light therapy may lead to therapeutic benefit for postpartum depression. Given that the potential risks associated with participating are minor and the potential benefits are considerable, it is believed that the risks are greatly outweighed by the benefits.



3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Establish the effect of wearable morning bright light therapy vs. dim light placebo on clinician-rated postpartum depression symptoms.	Hamilton Rating Scale for Depression 17—Item Version (HAMD-17) total score at post-treatment (week 5)
Establish changes in the phase angle difference (PAD) as a predictor of improvement in postpartum depression.	
Secondary	
Test the effect of morning bright light therapy on secondary outcomes (phase angle difference, self-reported depression, seasonal affective disorder symptoms, and maternal functioning).	Phase angle difference at post-treatment visit (week 5) Self-reported depression (EPDS total score) at post-treatment visit (week 5) Seasonal affective disorder symptoms (SIGH-SAD total score) at post-treatment visit (week 5) Daytime sleepiness (ESS total score) at post-treatment visit (week 5) Social functioning (SPSR total score) at post-treatment visit (week 5) Sleep-related impairment (SRI total score) at post-treatment visit (week 5) Social functioning (PBQ total score) at post-treatment visit (week 5)
Tertiary/Exploratory	
Examine self-reported depression and functioning at 3-months post-treatment.	Self-reported depression (EPDS total score) - at 3 month visit
Examine change trajectories by group over time for depression and seasonal affective disorder symptoms.	Daytime sleepiness (ESS total score) - at 3 month visit
Test the effect of morning bright light therapy on meal timing.	Social functioning (SPSR total score) - at 3 month visit Sleep-related impairment (SRI total score) - at 3 month visit
Test changes in dim light melatonin onset, chronotype, and sleep efficiency and total sleep time derived from wrist actigraphy as exploratory mediators for treatment response.	Social functioning (PBQ total score) - at 3 month visit HAMD-17 score - week 1 thru week 5 (week 1, 2, 3, 4, 5)

OBJECTIVES

ENDPOINTS

SIGH-SAD total score
- week 1 thru week 5 (week 1, 2, 3, 4, 5)
Meal timing (Eating Habits Questionnaire) at post-treatment visit (week 5)

4 STUDY DESIGN

4.1 OVERALL DESIGN

This trial utilizes a double-blind, randomized placebo-controlled study design. One-hundred twenty women who are ≤ 6 months postpartum and meet diagnostic criteria for an episode of major depressive disorder will be enrolled. Participants will be randomly assigned to 5 weeks of 60 mins of daily wearable morning bright light therapy (wBLT, $n = 60$) or wearable dim light placebo control (wDLT, $n = 60$). Self-reported outcome measures will be completed using a HIPAA-compliant data capture website, REDCap. Clinician-rated measures will be completed via secure videoconference or telephone, to minimize participant burden.

Aims and Hypotheses:

Aim 1: Establish the effect of wearable morning bright light therapy ($n = 60$) vs. dim light placebo ($n = 60$) on clinician-rated postpartum depression symptoms. Hypothesis 1. Relative to placebo, morning bright light therapy will produce greater improvement from pre- to post-treatment on the Hamilton Rating Scale for Depression (HAM-D-17) (primary outcome).

Aim 2: Establish changes in the phase angle difference (PAD) as a predictor of improvement in postpartum depression. Hypothesis 2. Relative to placebo, morning bright light therapy will lengthen the PAD and this will mediate change in depression symptoms.

Aim 3: Test the effect of morning bright light therapy on secondary outcomes (phase angle difference, self-reported depression, seasonal affective disorder symptoms, and maternal functioning). Hypothesis 3. Relative to placebo, morning bright light therapy will produce greater improvements on self-reported depression symptoms, seasonal affective disorder symptoms, excessive daytime sleepiness, maternal-infant bonding, social functioning, and sleep-related impairment from pre- to post-treatment.

Exploratory aims will examine (1) self-reported depression and functioning at 3-months post-treatment; (2) change trajectories over time by group for depression, seasonal affective disorder, and functioning; (3) the effect of bright light therapy on meal timing; and (4) DLMO, chronotype, and sleep efficiency derived from wrist actigraphy will be examined as exploratory mediators.

4.2 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 3-month post-treatment assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

We propose to enroll 120 women who are within 6 months postpartum and meet diagnostic criteria for an episode of major depressive disorder.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria: Females ≥ 18 years of age and (1) ≤ 26 weeks postpartum, (2) meet criteria for current major depressive disorder per the Structured Clinical Interview for DSM-V (SCID; [19]), (3) not currently receiving treatment for depression (i.e., prescription medications or psychotherapy)/no use of prescription medications for depression for the past 4 weeks, and (4) able to start light treatment at 5:00 am or later.

5.2 EXCLUSION CRITERIA

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

(1) Current diagnosis of PTSD, obsessive compulsive disorder if the onset is outside of the perinatal period, eating disorder, substance abuse or dependence, lifetime history of mania/hypomania or thought disorder per SCID, (2) current diagnosis of, or high risk for, sleep-disordered breathing (per STOP-BANG [20]), insomnia disorder (per SCID), restless leg syndrome (per SCID) and/or narcolepsy, (3) retinal pathology or history of eye surgery, (4) current use of photosensitizing medications, (5) current use of exogenous melatonin or medications that may interfere with the measurement of melatonin (NSAIDs if used daily, and beta-blockers), (6) medical conditions for which bright light therapy is contraindicated (e.g., epilepsy/seizures), (7) nightshift work, and (8) currently pregnant.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the emergence of depression for participants who did not meet criteria at the initial screening. Rescreened participants will be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will occur through multiple sites at Michigan Medicine, leveraging the existing research infrastructure of both the Michigan Medicine Obstetrics Department and the Michigan Medicine's Women's and Infants Mental Health Program (WIMHP), which encompasses both clinical care in Psychiatry and research on the unique mental health needs of perinatal women.

To recruit from the WIMHP Clinic, the WIMHP research coordinator sends the study coordinator weekly lists of scheduled new patient intakes, from which the study coordinator may contact patients directly or through their clinician. The WIMHP also maintains an IRB-approved research recruitment registry at 7 obstetrics clinics within Michigan Medicine. Briefly, all women who present for care at these clinics complete a screen consisting of a demographic form, perinatal depression measure (EPDS), and consent to be contacted for research.

Further, the Michigan Medicine Obstetrics Clinic maintains an IRB-approved biorepository, through which all women presenting for care complete a screen, which includes an item regarding their willingness to be contacted about research studies. The biorepository coordinator then sends a list of women who agree to be contacted to the study coordinator. As all women receiving care in the Obstetrics Clinic also complete

a depression screen (EPDS) as part of their clinical care, we are able to identify potential participants from the registry by querying their medical record to determine depression status.

We will utilize Data Direct on an ongoing basis to identify women who have given birth at Michigan Medicine to a single live infant and are within 6 months postpartum per diagnostic codes; these women will be sent an email introducing the study with a link to more information about the study and the online study screen if they are interested in participating.

Other recruitment strategies include flyers posted in Michigan Medicine Psychiatry and Obstetrics Clinics and listing the study in the University of Michigan Health Research Recruiting Registry.

We will also utilize The Michigan Institute for Clinical and Health Research's (MICHHR) Participant Recruitment (PR) service, which will assist in creation of flyers and other study advertisements, including creating, launching, and tracking Facebook advertisements.

Payment to participants is important to encourage participant participation and to compensate participants for the time required to participate in the study, especially as the saliva collection can take a bit of time and could require additional support for childcare during that time. Participants will be compensated with \$15 for the screening assessment. Once enrolled in the study, participants will receive \$100 for completing the first baseline sample collection, \$330 at the study midpoint, and \$270 after the post-treatment sample collection for adhering to treatment, sample collection, and completing outcome assessments. In addition, participants will receive an additional \$50 for completing measures via a secure website at 3-month follow-up. Finally, study staff will also contact participants via their preferred contact modality with reminders for their sample collections and follow-up assessments.

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

The study intervention is bright light therapy, administered via the Re-Timer®. The Re-Timer® delivers bright light through an eyeglasses interface, which allows for full ambulation during therapy, without concern for exposing others in the environment to light. The light is limited to the user's ocular area. Further, the device can be worn over eyeglasses, and does not interfere with vision, reading, or computer work. The Re-Timer® delivers blue-green light via LEDs (~500nm, 230 $\mu\text{W}/\text{m}^2$, 500 lux). Circadian photoreceptors are most sensitive to blue-green light in this wavelength (~480nm [21, 22]). The LEDs are positioned below the eyes and direct light upwards, so the supraorbital ridge does not block any of the light. Light from the Re-Timer® is UV-free, and the device has been independently tested for eye safety to the international standard CEI IEC 62471. Side effects of Re-Timer® are minor, consistent with those from light boxes, and include headache, eye irritation, and light bothersome to the eyes [23].

Participants assigned to the bright light condition will be provided with an active, unaltered Re-Timer® device to self-administer therapy. Participants assigned to the dim light condition will be provided with a placebo version of the Re-Timer® fitted with neutral density filters, which reduce the light intensity ($3\mu\text{W}/\text{m}^2$, 7 lux) to a level that does not shift circadian timing, even in light sensitive participants (i.e., individuals kept in dim light for several days; [24]). All participants will complete an item on the daily sleep diary to record the device on/off times. We will text reminders to participants to charge the device and

only turn it on during the scheduled time. All participants will also be provided with verbal and written instructions to minimize light exposure (especially from electronic devices) in the evening.

6.1.2 ADMINISTRATION AND/OR DOSING

Participants will use the Re-Timer daily for 5 weeks (approximately 35 days). All participants will be provided with a “light therapy window” during which they will wear the device for 60 mins. The device automatically turns off after 60 mins. The therapy window will be set using their average wake time from 1 week of baseline wrist actigraphy and sleep diary data, such that their treatment will start $\pm$ 30 mins from their average wake time in their baseline week. Minor adjustments to a participants’ light therapy window may be made based on clinical judgement and to accommodate unforeseen changes in participants’ schedules. All participants will complete an item on the daily light log to record the device on/off times.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Women who meet eligibility for the study will be randomized to either bright or dim light using the minimization method [25]. In this CONSORT-approved method, the first participant is truly random; thereafter participants are allocated to condition to minimize between-group imbalance of selected characteristics [26]. Minimization is a viable alternative to true randomization—arguably superior, as it allows for balanced groups even in smaller samples [27]. We will balance assignment to group based on the following baseline characteristics: baseline HAMD-17 score, maternal age, parity, and infant age. We will utilize the secure, web-based treatment assignment system implemented by the University of Michigan’s Consulting for Statistics, Computing, & Analytics Research service. The study coordinator will be responsible for randomization. Blinding. Participants and research staff assessing outcomes will be blind to treatment conditions to help ensure a rigorous and unbiased approach. The PI, study coordinator, and select research assistants will not be blind to condition as they will review Re-Timer® adherence data, which would unblind them to condition. Participants will be reminded at the outset of every outcomes assessment to not provide any information about the device or the treatment they are receiving.

6.3 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Adherence for participants in both conditions will be monitored using a light-sensing actigraph (Actiwatch Spectrum Plus (Philips Respironics, Bend, OR)) fixed to the inside of the device. As reviewed in the Preliminary Data section, this will allow for monitoring of device use. Participants will be told at the outset of the study that we are monitoring their adherence, and that they may be discontinued from study participation for non-compliance. Staff will contact participants daily by telephone or text message for the first 3 days to review adherence and address any emergent issues. Thereafter, participants will be provided the option to receive daily text or email reminders. Study staff will travel to participants’ homes at the treatment midpoint to download the actigraph data to a study laptop and review adherence to the treatment.

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

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance
- Lost-to-follow up; unable to contact subject (see **Section, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded in a participant withdrawal log. Participants who sign the informed consent form and are randomized but do not complete baseline assessments may be replaced. Participants who sign the informed consent form and are randomized and complete any of the baseline measures and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete 2 consecutive scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions will be taken if a participant fails to attend a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 attempts at contact). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Screening:

Participants will complete an initial eligibility screen through a secure website or via telephone. Those deemed to be eligible based on the initial screen will complete a second-level screen (virtual through a secure videoconference), where they will complete the full screening with trained research staff.

Objective Measures:

Salivary DLMO Collection. To objectively measure circadian timing, participants will undergo in-home salivary DLMO collection on one evening at baseline, mid-treatment, and post-treatment using the in-home collection kit and established protocol established by Co-I Dr. Burgess [28]. To minimize participant burden, study staff will travel to participants' homes to deliver the DLMO collection kit and review instructions in detail; they will also travel to participants' homes to collect the samples and equipment. Adequate dim light collection conditions are demonstrated during the home visit, verified by light meter. Participants are informed that we will be tracking their compliance to dim light conditions during collection and the time of sample collection. Participants will be in dim light starting 30 mins prior to the first sample

collection (i.e., 6.5 hours before habitual sleep onset). Collection begins 6 hours prior to participants' habitual sleep onset per most recent week of actigraphy and/or sleep diary; samples are collected via Salivette every 30 mins until bedtime (13 samples total). Minor adjustments to participants' bedtime on the DLMO night may be made to account for participant availability, and night-to-night variations in actigraphy data due to an unusual night of sleep that do not accurately reflect the participant's typical habitual sleep. The DLMO kit includes: a checklist of procedures; a pair of blue-blocking glasses, a test tube rack; a post-surgical toothbrush to remove food particles but also limit the potential for gum bleeding to contaminate the sample; a nightlight; a dimmed iPod Touch programmed to alarm with specific instructions at collection times; an Actiwatch Spectrum Plus worn around the neck using a lanyard to document compliance with dim light conditions; and pre-labeled salivette collection vials equipped with a MEMS Track Cap®, which will record when the vial was opened to determine compliance with time of sample collection. Participants remain seated in dim light throughout the protocol. When the iPod alarms, participants brush their teeth without toothpaste, collect saliva by chewing on the salivette and deposit it in the vial. Samples will be stored in participants' freezers until they can be transported to our facility. Saliva samples will be centrifuged, frozen, and shipped on dry ice to SolidPhase, Inc (Portland, ME), which performs the direct Buhlmann RIA assay with sensitivity of 0.5 pg/ml, and intra- and inter-assay CV <7.5% at 3 pg/ml [29, 30].

Maternal Wrist Actigraphy. Participants will wear actigraphs on their wrist for approximately 4-7-days at baseline, mid-treatment, and the final treatment week. The actigraph (Actiwatch Spectrum Plus, Philips Respironics, Bend, OR) is a small waterproof device the size of a wristwatch (48 x 37 x 14 mm weighing 30 grams) that is worn continuously on the non-dominant wrist. A solid-state piezo-electric accelerometer (range 0.5-2G peak value, sensitivity 0.025G) integrates movement frequency and intensity into a single measurement. In addition, color-sensitive photodiode sensors (range 400-700 nm) continuously monitor incoming light and store the data in lux levels. The actigraphs are set at a sampling rate of 30 seconds. Activity and light data are downloaded to a computer and sleep/wake activity is estimated by Actiware®–Sleep software using published guidelines, confirmed using sleep diary when necessary. Actigraphy has been used extensively in studies of postpartum women. The following variables will be derived from the sleep assessments: midpoint of sleep, total sleep time, and sleep efficiency. Midpoint of sleep per actigraphy will be used to characterize sleep timing for the PAD calculation.

Infant Actigraphy. Infant sleep-wake patterns will be used as covariates in analyses. Infant sleep-wake patterns will be objectively assessed using actigraphy (Actiwatch-2; Philips Respironics, Bend, OR) worn on the infant's left ankle for at least 4 days during the baseline, mid-point, and the final treatment week. Sleep/wake activity will be estimated using Actiware®–Sleep software using published guidelines for infants younger than 6 months [31]. To assist in actigraphy scoring, participants will also be asked to maintain a daily sleep-wake log for their infants. The following variables will be estimated from infant actigraphy: infant sleep period, infant sleep time, infant night wakings, longest sleep period.

Self-report Measures:

All self-report measures will be completed by participants via a secure website through REDCap (Research Electronic Data Capture), a secure HIPAA-compliant web application that facilitates the collection and entry of research data. Participants who do not have internet access will be provided with paper and pencil versions of the measures to complete and return via self-addressed, postage-paid envelope.

Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a self-report measure of perinatal depression symptoms that will be completed at baseline, weekly through treatment, and at the 3-month

follow-up. The EPDS has good sensitivity and specificity to detect depression in postpartum women. Depression remission status will be determined using established cut-off score. The sleep items will be removed from the EPDS total score calculations.

Sleep Diary. At their baseline visit a member of the study team will instruct the participant on how to keep an accurate daily sleep diary. They will complete the consensus sleep diary daily for approximately 4-7 days at baseline, mid-treatment, and post-treatment. As in our previous studies, women will be instructed to omit periods during the night spent caring for the infant (or other children) from the diary.

Epworth Sleepiness Scale (ESS). The ESS is a widely used, reliable measure of daytime sleepiness, completed at baseline, treatment midpoint, post-treatment, and at 3-month follow-up. A score of ≥ 10 indicates excessive daytime sleepiness on the ESS.

Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment Short Form (SRI). To measure daytime impairment due to sleep, participants will complete the PROMIS SRI. The SRI is a brief, valid, self-report measure of daytime impairment due to sleep disturbance and will be completed at baseline, treatment midpoint, post-treatment, and at 3-month follow-up.

PROMIS Satisfaction with Participation in Social Roles (SPSR). To measure social functioning, participants will complete the SPSR, a measure of satisfaction with participation in social roles. The SPSR is a brief, valid, and efficient measure of social functioning that is also sensitive to clinical change in adults with depression. It will be completed at baseline, treatment midpoint, post-treatment, and at the 3-month follow-up.

Postpartum Bonding Questionnaire (PBQ). The PBQ is a self-report measure of maternal-infant bonding and has good reliability and validity for assessing impairment in maternal-infant bonding. It will be completed at baseline, treatment midpoint, post-treatment, and at the 3-month follow-up.

Treatment Evaluation. Treatment expectation will be assessed at baseline and post-treatment using The Reaction to Treatment Questionnaire [32]. Treatment satisfaction will be measured at post-treatment with the Client Satisfaction Scale [33]. They will also be provided with a treatment satisfaction questionnaire comprised of open-ended questions about acceptability, adherence, and what they liked and what they would change about treatment. At the 3-month follow-up, participants will be asked to complete a short questionnaire assessing whether they have sought out treatment for depression, and whether they have used light therapy since they completed the treatment phase of the study.

Dietary Screener Questionnaire (DSQ). The dietary screener questionnaire is 26 item questionnaire that asks about the frequency of consumption in the past month of selected foods and drinks. The DSQ captures intakes of fruits and vegetables, dairy/calcium, added sugars, whole grains/fiber, red meat, and processed meat. The DSQ will be used as a covariate in the exploratory meal timing aim.

Eating Habits Questionnaire. The eating habit questionnaire assesses eating frequency, timing and quality in parts referring to Nutricalc questionnaire. For the present study, we are using only the first 3 items of this questionnaire, which are focused on the frequency and timing of meals.

Morningness-Eveningness Questionnaire (MEQ). The Morningness-Eveningness Questionnaire [37] consists of 19 self-report questions that ask about bedtimes and waking times, preferred times for activities and alertness. The MEQ will be completed at baseline, treatment mid-point, post-treatment, and

at the 3-month follow-up.

Clinician-rated Measure:

Hamilton Rating Scale for Depression. The Hamilton Rating Scale for Depression will be administered by a clinician (Seasonal Affective Disorders Version, SIGH-SAD). From the SIGH-SAD, we will derive a total score for depressive symptoms (Hamilton Rating Scale for Depression 17-item scale, HAMD-17) as well as a total score for seasonal affective disorder symptoms (SIGH-SAD, 29 items). The SIGH-SAD will be administered by a study clinician to study participants via telephone or secure videoconference weekly through treatment. Note that SIGH-SAD administrations will be recorded, with 40% of these recordings randomly selected for fidelity checks.

8.2 SAFETY ASSESSMENTS

Side Effects. Participants will complete a modified version of the Systematic Assessment of Treatment Emergent Events (SAFTEE) questionnaire weekly throughout the treatment period to evaluate for any side effects of the intervention. The SAFTEE will be modified to include only relevant symptom domains.

Columbia Suicide Severity Rating Scale (CSSRS). Suicidal ideation will be assessed using the clinician-rated CSSRS. A study clinician will administer the CSSRS to study participants weekly through treatment, during the same telephone/videoconference meeting as the SIGH-SAD.

Medications. Participants will complete a medication form at baseline and weekly throughout the treatment period to assess for any changes to medication usage throughout the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoints:

1. We hypothesize that, relative to dim light placebo, morning bright light therapy will produce greater improvement from pre- to post-treatment on the Hamilton Rating Scale for Depression 17-item total score (HAMD-17) (primary outcome).
2. We hypothesize that, relative to placebo, morning bright light therapy will lengthen the PAD and this will mediate change in depression symptoms.

Secondary Endpoints:

1. We hypothesize that, relative to placebo, morning bright light therapy will lengthen the PAD and produce greater improvements on self-reported depression symptoms, seasonal affective disorder symptoms, excessive daytime sleepiness, maternal-infant bonding, social functioning, and sleep-related impairment from pre- to post-treatment.

Exploratory Endpoints:

1. We hypothesize that, relative to placebo, morning bright light therapy will produce greater improvements in self-reported depression symptoms, excessive daytime sleepiness, maternal-infant bonding, social functioning, and sleep-related impairment at 3-months post-treatment.
2. Change trajectories over time by group for depression, seasonal affective disorder, and functioning.
3. The effect of bright light therapy on meal timing.

Exploratory Mediators:

Change in phase angle difference, dim light melatonin onset, chronotype, total sleep time, and sleep efficiency derived from wrist actigraphy will be tested as exploratory mediators for change in depression symptoms.

9.2 SAMPLE SIZE DETERMINATION

Power analyses were completed using NQuery 2017. We have conservatively estimated power for traditional analytic approaches (i.e., Student's t-tests) without accounting for linear mixed model methods, which will allow for inclusion of participants with partial data, or for the gains in power generated by the use of repeated measures. The study is powered to be sensitive enough to detect the smallest clinically meaningful difference in the HAMD-17 of 3 points [34]. With a standard deviation of 5 (per baseline HAMD-17 from a postpartum depression clinical trial), a sample of 45/group would allow us to detect a 3-point difference at post-treatment between groups at 80% power for a two-tailed $\alpha=0.05$ test. Thus, our proposed sample of 60 per group ($n = 120$ total), allowing for a 25% attrition rate, should be sufficiently powered to test our hypotheses.

Power for mediation was assessed using a simulated design with a final sample of 90 subjects observed at three time points (pre-, mid-, and post-treatment), in three mediation strength settings: low (~33%), moderate (~58%), and high (~81%) mediation. Power for detecting non-zero mediation exceeded 80% for the moderate and high, but not the low setting. Our proposed sample will therefore be sufficiently powered to detect mediation if PAD is an important mechanism in the pathway. If PAD is a low strength mediator in this study, the result is still informative, as it suggests an alternative mechanism, and we will test possible alternative mechanisms, including DLMO and sleep efficiency. The average confidence interval widths for assessing the proportion of mediation were 0.64, 0.41, and 0.24, in the low, medium, and high settings, respectively. That is, when the true proportion of mediation is high, the 95% confidence interval for the proportion of mediation would on average be the estimate ± 0.12 .

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Populations for Analyses

Four study populations are defined for these analyses:

- **Intention-to-Treat (ITT):** The intention-to-treat (ITT) population includes all subjects who were randomized and participated in the bright light therapy (treatment) or dim light therapy (placebo) for at least one week. Subjects will be analyzed by assigned treatment. This population will be used for sensitivity analyses of the primary efficacy endpoint (if it differs from the MITT population).
- **Modified Intention-to-Treat (MITT):** The main population for efficacy analyses will be the modified intention-to-treat population (MITT), defined as all subjects randomized, and participated in the bright light therapy (treatment) or dim light therapy (placebo) for at least one week, and having at least one post-baseline SIGH-SAD assessment. Subjects will be analyzed by assigned treatment. In any specific MITT analysis, imputation strategies (defined within specific analyses) will be considered for subjects with missing outcomes.

- **Per Protocol:** The Per Protocol population (PP) will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of violation of entry criteria. This population will be used for sensitivity analyses of the primary efficacy endpoint. Subjects in this population will be referenced as evaluable. Missing values will not be imputed for the per-protocol population; rather, subjects with missing outcomes will be excluded from analyses.

Protocol deviations will be reviewed prior to database lock and designated as major or not major. Major protocol deviations include:

- o Significant and persistent treatment adherence issues
 - o Error in randomization (i.e., received wrong intervention or placebo allocation)
 - o Subject did not meet eligibility criteria and does not have a waiver
- **Safety Population:** The Safety Population is defined as all subjects who were randomized and participated in bright light therapy (treatment) or dim light therapy (placebo) for at least one week. The Safety Population will be used for all safety analyses, as well as subject disposition, demographic and baseline analyses. Subjects will be analyzed by treatment received for safety outcomes.

Note that the number of subjects in the ITT and Safety Populations are equivalent. A difference between the populations used for efficacy outcomes (ITT, MITT, PP) and safety outcomes (Safety) is that treatment groups are analyzed by the assigned treatment for efficacy and by the actual treatment received for safety.

The primary endpoint (HAMD-17 total score at post-treatment, week 5) and important covariates (baseline HAMD-17 total score, maternal age, parity, and infant age) will be considered for multiple imputations. For secondary endpoints and important covariates, multiple imputation methods will also be considered. The MITT population will be used for the secondary analyses. Missing data will be handled using either multiple imputations, or sensitivity analysis. We expect much of the missing data to not be missing at random, so the multiple imputations will not be used in those cases.

Several analysis sets will be used in analyses:

- The main population for efficacy will be the modified intention-to-treat population (mITT), defined as all participants randomized and receiving at least one week of a study intervention. Subjects will be analyzed by assigned treatment.
- A second analysis set will be used to assess the robustness of the primary conclusions in the subset of participants in the mITT analysis set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effect of treatment according to the underlying scientific model. The Per Protocol (PP) analysis set will consist of all subjects in the mITT population who do not have a major protocol violation, inclusive of violation of entry criteria.
- The Safety Population is defined as all participants who are randomized and receive at least one week of study intervention. The Safety Population will be used for any safety analyses conducted. Subjects will be analyzed by treatment administered.

Statistical Analysis

All hypothesis testing will use two-sided tests and p-values <0.05 will be considered significant. Analyses

will begin with descriptive examinations (plots) of distributions of key variables to identify missing data, review data for outliers and anomalies. Tests for linearity, independence, missingness, and distributional assumptions will be performed. Normalizing transformations will be utilized as needed. Prior to fitting any analytic models, a graphical exploration of the outcome variables will be conducted.

Missing data. To minimize missing data, we will make every effort to retain all participants using strategies that have proven successful in our prior research. When necessary, we will perform multiple imputations of missing data and combine the results from the multiply imputed datasets. For exploratory outcomes, it is also important to note that the proposed mixed effects regression modeling will allow for the use of data from all participants (including those with missing outcome data) and provide unbiased parameter estimates that account for missing data under the missing-at-random assumption [36]. We will also examine for non-random attrition.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Aim 1. Establish the effect of wearable bright light therapy vs. dim light placebo on clinician-rated postpartum depression symptoms.

Primary endpoint: ANCOVA (Analysis of covariance) will be conducted on the post-treatment (week 5) HAMD-17 total score outcome with adjustment for pre-treatment (baseline) HAMD-17 total score and covariates known to be strongly associated with postpartum depression (i.e., parity).

Aim 2. Establish changes in phase angle difference as a predictor of improvement in postpartum depression.

Primary endpoint: If a significant effect is detected (at a $p < 0.05$ level) for the Aim 1 ANCOVA analysis of the HAMD-17 outcome, mediation analysis with change in phase angle difference as a mediator will be assessed

Mediation: Analyses for mediation will include post-treatment week 5 PAD (mediator), post-treatment week 5 HAMD-17 total score, adjustment for pre-treatment (baseline) PAD and covariates known to be strongly associated with postpartum depression (i.e., parity). We will test for mediation using a causal inference or “counterfactual” approach, as described by Valeri and Vanderweele [37] (133), and previously used by our group in other investigations [38].

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Aim 3. Test the effect of morning bright light therapy on secondary outcomes (self-reported depression, seasonal affective disorder symptoms, and maternal functioning).

Secondary endpoint: ANCOVA analyses analogous to methods detailed for the Aim 1 primary endpoint (HRSD total score week 5 post-treatment) will be conducted using EPDS, ESS, PBQ, SRI, SPRS, and SIGH-SAD total scores at 5 weeks post-treatment.

9.3.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Exploratory Aim 1: Examine self-reported depression and functioning at 3-months post-treatment.

Exploratory endpoints: ANCOVA analysis analogous to methods detailed for the Aim 1 primary endpoint (HRSD total score week 5 post-treatment) will be conducted using EPDS, ESS, PBQ, SRI, and SPRS total scores at the 3-month post-treatment time point.

Exploratory Aim 2: Examine change trajectories by group over time for depression and seasonal affective disorder symptoms. Exploratory endpoint: Mixed-effects repeated measures models will be fitted for the HAMD-17 score and the SIGH-SAD total scores (week 1 thru week 5, minus the sleep items) as a dependent variable with adjustment for pre-treatment (baseline) scores (HAMD-17 and SIGH-SAD) and covariates known to be strongly associated with outcomes (i.e., parity). This will be conducted to examine interaction between treatment and time from week 1 through week 5.

Exploratory Aim 3: Test the effect of morning bright light therapy on meal timing.

Exploratory endpoints: ANCOVA analysis analogous to methods detailed for the Aim 1 primary endpoint (HAMD-17 total score week 5 post-treatment) will be conducted using meal timing at 5 weeks post-treatment). Additionally, DHQ will be included as a covariate.

Exploratory Aim 4: Test changes in dim light melatonin onset, chronotype, total sleep time, and sleep efficiency derived from wrist actigraphy as exploratory mediators for treatment response.

Exploratory endpoints: Analysis for mediation analogous to methods detailed for the Aim 2 endpoint (PAD week 5 post-treatment) will be conducted using dim light melatonin onset, chronotype, total sleep time, and sleep efficiency.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The consent process may be completed via secure videoconference or in-person.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

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

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.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

After the study is completed, the de-identified, archived data will be transmitted to and stored at the National Institute of Mental Health Data Archive for use by other researchers including those outside of the study. Permission to transmit data to the National Institute of Mental Health Data Archive will be included in the informed consent. When the study is completed, access to study data will be provided through the National Institute of Mental Health Data Archive.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with appropriate expertise, including perinatal mental health. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the IRB and National Institutes of Health staff.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

Source documents and the electronic data – Data will be captured directly from participants and the study clinician using REDCap (Research Electronic Data Capture) system, a secure web application.

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

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of study staff under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All data will be collected via REDCap, a secure web application, compliant with 21 CFR Part 11. Data will be entered directly by participants as they complete measures, and by study clinicians as they complete clinician-rated measures.

10.1.8 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a

result of deviations, corrective actions will be developed by the investigator and implemented promptly as needed. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.9 PUBLICATION AND DATA SHARING POLICY

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

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

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by through the NIMH Data Archive. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.2 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption

IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

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

Version	Date	Description of Change	Brief Rationale
3.0	5/12/2021	1.3 Schedule of Activities, Sections 3, 8, and 9.3.3	The following additions were made: an exploratory aim; and The Dietary Screener Questionnaire and Eating Habits Questionnaire were added to the study assessments.
3.0	5/12/2021	2.3.3 Assessment of Potential Risks and Benefits	The following changes were made to safety monitoring plan: adjust worsening of depression criteria; include additional trigger items on SAFTEE adverse events assessment.
4.0	7/29/2021	2.3. Assessment of Potential Risks and Benefits	To ensure we are only capturing treatment-emergent adverse events on the SAFTEE and to have some flexibility with personnel who are able to contact participants to follow-up on adverse events.
4.0	7/29/2021	4.1 Overall Design	Clarification of which aims/objectives/endpoints are exploratory.
4.0	7/29/2021	5.1-5.2 Inclusion/Exclusion criteria	To ensure we are not enrolling participants who have circadian rhythms impacted by either an early rise time or nightshift work.
4.0	7/29/2021	5.4 Strategies for Recruitment and Retention	To enhance recruitment.
4.0	7/29/2021	6.3 Study Intervention/Experimental Manipulation	Reduce participant burden by giving them an option for us to contact them via text message instead of telephone.
4.0	7/29/2021	8.2 Safety Assessments	Modify items administered on SAFTEE to only include those relevant to light therapy. Reduce participant burden given the large number of items that are not relevant to light therapy.
4.0	7/29/2021	9 Statistical Considerations	Minor modifications to statistical considerations. As recommended by the study statistician.

5.0	2/8/2022	1.3 Schedule of Activities (These changes are also made in section 8.1 Endpoint and Other Non-Safety Assessments and 8.2 Safety Assessments): Change frequency of sleep diary from daily to 4-7 days at baseline, mid-, and post-treatment timepoints. Change number of days of infant actigraphy obtained to be more flexible (4-5 days). Add the Medications List assessment.	To reduce participant burden, limit unnecessary protocol deviation reporting (4 days of infant actigraphy is valid), and to ensure participants are not starting new medications that are not allowed.
5.0	2/8/2022	2.3.3 Assessment of Potential Risks and Benefits: Adjusted SAFTEE items to only include those most relevant to light therapy.	To reduce participant burden.
5.0	2/8/2022	5.2 Exclusion Criteria: Added currently pregnant	To ensure we are enrolling women who are postpartum only.
5.0	2/8/2022	6.1.2 Administration and/or Dosing: Specify that minor adjustments may be made to a participants' light therapy window based on clinical judgement/accommodate participants' schedules.	Such flexibility is needed to ensure we are setting a window that the participants can follow.
5.0	2/8/2022	7.1. Participant Discontinuation/Withdrawal from the Study: Specify that participants who sign the informed consent form, are randomized, and complete baseline measures will not be replaced.	Participants who complete baseline measures will be utilized in the full dataset and therefore will not be replaced.
6.0	4/29/2022	Included the MEQ as a study assessment to the following sections: 1.3 Schedule of Activities, 3.0 Objectives and Endpoints, and 8.1 Endpoints and Other Non-Safety Assessments	To collect information on changes to chronotype as an exploratory aim.
7.0	12/16/2022	Inclusion criteria #1 was changed from ≤ 24 weeks postpartum to ≤ 26 weeks postpartum	The study is focused on population is women within 6 months postpartum (which is technically a period of 0-26 weeks and

			would correspond to an infant of 0-26 weeks' age); however, the inclusion criteria in our protocol incorrectly identified infant age for eligibility to be ≤ 24 weeks of age.
8.0	2/14/2023	8.1 Study Assessments and Procedures (page 18) At the 3-month follow up, participants will be asked to complete a short questionnaire assessing whether they have sought out treatment.	To collect information regarding a variable that may influence the 3-month follow-up findings.
9.0	5/15/2023	5.2, Exclusion criteria Amended criteria to indicate that current obsessive-compulsive disorder (OCD) is exclusionary only if onset occurs outside of the perinatal period.	The justification for this change is that perinatal OCD is common, and different from OCD which occurs outside of the perinatal period in that the symptoms are often more circumscribed (focused on the infant) and typically self-limiting/resolves without treatment with time.
10.0	10/25/2023	5.2, Exclusion criteria The assessment used to assess restless leg syndrome (RLS) from the Cambridge-Hopkins diagnostic questionnaire to RLS questions taken based on the Diagnostic and Statistical Manual of Mental Disorders-5 th Edition diagnostic criteria to update our assessment to a scheme that includes frequency and duration of symptoms.	The assessment used to assess restless leg syndrome (RLS) from the Cambridge-Hopkins diagnostic questionnaire to RLS questions taken based on the Diagnostic and Statistical Manual of Mental Disorders-5 th Edition diagnostic criteria to update our assessment to a scheme that includes frequency and duration of symptoms.

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