Preventing Depressive Relapse in Pregnant Women With Recurrent Depression

NCT03623620

5/17/2021

PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

I. BACKGROUND AND SIGNIFICANCE

UPWARD Study

Historically, pregnancy has been viewed as a protective time with respect to risk for psychiatric illnesses. This assumption, along with ethical concerns regarding the conduct of randomized trials during pregnancy, has resulted in limited evidence regarding how to best manage depression during pregnancy. In contrast, robust evidence indicates that depression is prevalent during pregnancy and is associated with increased risk of adverse correlates and consequences for offspring, including obstetrical and neonatal outcomes such as shorter gestational age, increased rates of preterm delivery and lower birthweight; affective and behavioral dysregulation during childhood; and increased risk for later psychopathology[1-3]. The most robust predictor of depression during pregnancy is history of depression, and women with recurrent depression experience high rates of relapse depression during pregnancy[4,5], underscoring the pragmatic and ethical need for definitive evidence regarding how to mitigate risk of depressive relapse during this important developmental transition.

The current treatment guideline and standard of care for preventing depressive relapse among adults with a history of recurrent major depressive disorder (MDD) is maintenance antidepressants (AD), which poses unique challenges for the management of depression for pregnant women with recurrent depression[6-9]. Decisions regarding maintenance relative to discontinuation of AD during pregnancy require a weighing of increased risk of relapse associated with AD discontinuation, on one hand, versus the known and unknown risks of fetal exposure to AD on the other. Rates of subsequent relapse are significantly higher among women with recurrent depression who discontinue AD than among those who maintain, and depression during pregnancy is one of the greatest risk factors for postpartum depression[10,11]. Postpartum depression not only places the mother at risk for refractory illness, but also can have long-term negative consequences on child development and behavior[12,13].

Prior work has demonstrated that a non-pharmacologic intervention, Mindfulness-Based Cognitive Therapy (MBCT), modified for pregnant women, yields significant reduction of depressive relapse risk and symptom burden versus usual care through six months postpartum[14] and is feasible to deliver digitally[15,16]. However, the precise role of non-pharmacologic interventions like MBCT as an alternative to AD is unclear, leaving pregnant women with recurrent depression and their providers in the position of making critical clinical decisions with incomplete evidence to guide them. There is an urgent need for systematic, practical, and personalized guidance to support decision-making among women and their healthcare providers, to determine if MBCT offers benefit with respect to usual care (UC) in community practice settings, and to determine what approach is most likely to confer the greatest benefit and least risk for a given woman and her child.

Multiple randomized controlled trials have demonstrated comparable relapse protection among patients randomized to MBCT vs. maintenance AD, a finding of central interest to reproductive aged women and their healthcare providers. However, there are indications that outcomes are moderated by baseline patient characteristics. For example, Segal et al. reported that MBCT and maintenance AD performed comparably and significantly better than placebo specifically among patients with residual depressive symptoms[17]. Williams and colleagues reported that MBCT, compared to an active psychoeducational control, was efficacious in preventing relapse specifically among a subsample of participants who reported early abuse[18], a pattern that was also observed in a comparison of MBCT and maintenance AD in which MBCT

was superior to AD specifically among this subgroup[19]. Preliminary analyses from DeRubeis et al. applied the Personalized Advantage Index (PAI)[20] method to a randomized trial of MBCT vs. maintenance AD, with results indicating that the decision of MBCT versus maintenance AD must be personalized.

We propose to address a significant gap in the evidence regarding effective approaches to prevent depressive relapse among women with recurrent depression who maintain euthymia using AD and who wish to conceive or who are pregnant. Relapse rates of depression following AD discontinuation among such women has been established[10], and the efficacy of MBCT in mitigating relapse risk in pregnant women with recurrent depression compared to UC also has been demonstrated[14]. But the effectiveness of MBCT has not been tested in a definitive trial; the question of whether MBCT can mitigate risk for depressive relapse among pregnant women on AD, including among those who discontinue AD proximate to or during pregnancy, also has not been addressed. Reproductive age women with recurrent depression and their healthcare providers need to know, first, if a scalable digital non-pharmacologic prevention approach is superior to UC in community settings, and second, whether MBCT can attenuate risk for depressive relapse among those who elect to discontinue maintenance AD treatment proximate to or during pregnancy. Lastly, the capacity to identify which women are most likely to benefit from a non-pharmacologic or pharmacologic approach personalizes the risk benefit decision making process for reproductive age women on AD planning to conceive or who are pregnant.

UPWARD Supplemental Arms (UPWARD-S)

The prevalence of suicidal ideation and behavior among perinatal women has been reported to be 5-14%.[3] Precise estimates of suicidal ideation and behavior during pregnancy are still unclear and may vary based on presence of prior psychiatric illness.[4-7] Because suicidal ideation and behavior are associated with multiple adverse correlates and consequences among perinatal women, including being among the leading causes of maternal mortality,[8] it is critical to understand the prevalence, severity, longitudinal course, correlates and predictors of suicidal ideation and behavior among women during pregnancy and the postpartum period.

With respect to characteristics, correlates and course, prior work has provided a strong foundation for selection of candidate clinical and demographic variables, most of which we already assess in our parent trial.[3,4,7,9-12] Exposure to stress also has been identified as an important correlate and predictor. Adverse childhood experiences have been noted as correlates of suicidal ideation,[4,17,18] as has current intimate partner abuse.[19,20] We can leverage assessment methods already included in our parent trial and related studies to investigate multivariate correlational and predictive models to better understand and potentially prevent suicidal ideation and behavior among pregnant and postpartum women.

Mindfulness Mood Balance for Moms is a promising, scalable non-pharmacologic digital program to address the needs of pregnant women with recurrent depression and suicidal ideation. Recent reviews have called for additional research examining mindfulness-based interventions among adults with suicidal ideation and behavior.[26] These recommendations are based, in part, on studies of mindfulness-based cognitive therapy (MBCT) among adults with histories of suicidal ideation and behavior.[16,27-29] Additionally, some evidence suggests specific processes by which these benefits may be conferred in MBCT, such as meta-awareness, specificity of autobiographical memory,[15,16] the strengths of association between depression symptoms and suicidal thoughts,[32] and asymmetry in resting EEG activation.[33] Given this evidence, MMB for Moms may be a promising intervention for pregnant women with suicidal ideation, as it delivers digitally both the content and structure of in-person MBCT. It is necessary to explore qualitatively the extent to which adaptations to the standard MMB for Moms program may be necessary to maximize engagement of pregnant women with suicidal ideation and behavior and to examine feasibility and acceptability in pilot work.[35]

Our understanding of community provider knowledge and skill in managing suicidal ideation and behavior among pregnant women is limited. Many women who screen positive for significant depressive symptoms during pregnancy fail to be referred for treatment and among those who receive treatment, the interventions received are not associated with restoration of euthymia.[21] Within the general population, qualitative methods have been informative in understanding models of care,[23] provider training on suicide and self-harm risk assessment,[24] policies for supporting patients at risk for suicide,[24] referral processes,[23] interventions for suicide prevention,[23] access to mental health providers within the health setting,[25] perceptions regarding the importance of patient access to a mental health provider for comprehensive care,[25] barriers and challenges to providing patients with care,[23] support available for providers following the death of a patient by suicide,[24] and personal experiences with mental health.[25] It is critical to understand the knowledge and resources in community settings that care for perinatal women to inform future health service and provider education efforts.

II. SPECIFIC AIMS

UPWARD Study

Objective: The overarching objective of this investigation is to conduct a pragmatic effectiveness trial comparing Mindful Mood Balance for Moms (MMB), a digital MBCT program, plus UC to UC only among euthymic pregnant women with recurrent depression treated with AD.

Aim 1: To test the relative risk for depressive relapse and reduction of symptom burden between women randomized to digital MMB or UC.
Hypothesis 1: We predict that relative risk for depressive relapse and reduction of symptom burden will be significantly lower among women randomized to digital MMB relative to women randomized to UC.

Aim 2: To explore the specific benefit of MMB relative to AD discontinuation and questions regarding personalization that are of strong interest to pregnant women and their healthcare providers.
Hypothesis 2a. We predict that relapse risk and symptom burden among women who discontinue AD will be significantly lower among those randomized to MMB than UC.
Hypothesis 2b. Considering women randomized to MMB who discontinue AD and women randomized to UC who maintain AD, we predict that a treatment selection algorithm will identify which approach works best for whom (baseline characteristic profiles) and that women who receive the algorithm indicated approach will have superior outcomes to those who receive the algorithm contraindicated approach.

Aim 3: To test the extent to which digital MMB engages putative targets.
Hypothesis 3: We predict that women randomized to MMB will show significantly greater improvement in maladaptive cognitive processing (i.e., reduced rumination, increased mindfulness and self-compassion) than women randomized to UC and that these changes will mediate relapse prevention.

UPWARD Supplemental Arms

Objective: In the supplemental arms we will investigate the prevalence, severity, longitudinal course, correlates and predictors of suicidal ideation and behavior among women during pregnancy and the postpartum period (Arm 1a). We will also examine the safety, feasibility, and acceptability of enrolling pregnant women with suicidal ideation in our parent trial of MMB compared to usual care (Arm 2). Additionally, we will describe the resources for responding to suicidal risk that are available for pregnant and postpartum women in community settings and the experiences of healthcare providers who provide care to these women during such a critical time in their lives (Arm 1b). We will lastly use a cross-sectional design to describe the characteristics and correlates of suicidal ideation and behavior among pregnant women (Arm 1c).

Arm 1: We will characterize a real-world population of pregnant and postpartum women by describing the characteristics, correlates, course, and predictors of suicidal ideation and behavior using mixed-methods in the context of cross-sectional and longitudinal designs.

Aim 1a. Using a prospective longitudinal design, we will describe the characteristics, correlates, course, and predictors of suicidal ideation and behavior among pregnant and postpartum women using clinical and qualitative interviews, self-report instruments, behavioral task, and medical records from community providers (n = 125).

Aim 1b. Using qualitative interviews, self-report instruments, and medical records, we will describe the extent to which community healthcare professionals providing care to pregnant and postpartum women with suicidal ideation report the knowledge base and requisite skills to address suicidal ideation and behavior in the real-world population of healthcare providers serving the sample of women enrolled in Aim 1a (n = 125).

Aim 1c. Using a cross-sectional design, we will describe the characteristics and correlates of suicidal ideation and behavior among pregnant women (n = 550).

Arm 2 (**Aim 2**): Using expanded entry criteria in our parent grant pragmatic trial design, we will explore the safety, feasibility, and acceptability of expanding study entry criteria specifically to enroll pregnant women with any reports of suicidal ideation or behavior (n = 40) in a proof of concept randomized controlled trial of MMB for Moms to enhanced usual care.

III. SUBJECT SELECTION

UPWARD and UPWARD Extension

Inclusion Criteria

1) Pregnant women (prior to 16 weeks' gestation)
2) Age 18 or older
3) History of recurrent major depression prior to pregnancy (at least two prior episodes, one of which may be currently treated)
4) Euthymic or with residual symptoms (PHQ9 ≤ 9)
5) No depressive relapse since the last menstrual period (LMP)

6) Currently or recently receiving antidepressants (at most 12 weeks prior to LMP)

7) Presence of an ongoing community prescriber/provider

Exclusion Criteria

1) Diagnosis of bipolar or psychotic disorder

2) Mania, psychosis, or active substance abuse (within last 6 months for substance abuse)

3) Immediate risk of self-harm

4) Non-English speaking

Drop Criteria

1) Inability or unwillingness to complete study procedures

2) Suicide attempt made during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of the attempt.

3) Psychiatric hospitalization during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of being discharged.

4) Miscarriage or termination of pregnancy

UPWARD-S

Arm 1 Aim 1a

Inclusion Criteria

1) Pregnant women (prior to 16 weeks' gestation)

2) Age 18 or older

3) Presence of an ongoing community prescriber/provider

4) suicidal ideation as noted by item #9 of the PHQ-9

5) History of recurrent depression, dysthymia, or subsyndromal depression

Exclusion Criteria

1) Diagnosis of bipolar or psychotic disorder

2) Mania, psychosis, or active substance abuse (within last 6 months for substance abuse)

3) Non-English speaking

Drop Criteria

1) Inability or unwillingness to complete study procedures

2) Suicide attempt made during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of the attempt.

3) Psychiatric hospitalization during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally upon discharge as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of being discharged.

4) Miscarriage or termination of pregnancy

Arm 1 Aim 1b

Inclusion Criteria

1) Age 18 or older

2) Current prenatal healthcare provider of a participant enrolled in Arm 1 Aim 1a

Exclusion Criteria

1) Non-English speaking

Arm 1 Aim 1c

Inclusion Criteria

1) Pregnant women
2) Age 18 or older

3) Self-reported history of major depressive disorder

4) suicidal ideation as noted by item #9 of the PHQ-9

Exclusion Criteria

1) Non-English speaking

Arm 2

Inclusion Criteria

1) Pregnant women (prior to 16 weeks' gestation)
2) Age 18 or older
3) History of recurrent major depression prior to pregnancy (at least two prior episodes, one of which may be currently treated
4) Euthymic or with residual symptoms (PHQ9 ≤ 9)
5) Presence of an ongoing community prescriber/provider
6) Current suicidal ideation as noted by item #9 of the PHQ-9 or past suicidal ideation as noted by item A3g on the MINI Mood module

Exclusion Criteria

1) Diagnosis of bipolar or psychotic disorder
2) Mania, psychosis, or active substance abuse (within last 6 months for substance abuse)
3) Non-English speaking

Drop Criteria

1) Inability or unwillingness to complete study procedures
2) Suicide attempt made during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of the attempt.
3) Psychiatric hospitalization during the course of the study if they do not have the appropriate psychiatric/behavioral health care in place locally as determined by a study physician. To be considered appropriately cared for, participants must be able to identify at least 1 mental health or prenatal provider by name and have an appointment scheduled with an outpatient provider within 10 days of being discharged.
4) Miscarriage or termination of pregnancy

All recruitment will be conducted digitally in collaboration with BabyCenter. BabyCenter will utilize established methods to engage pregnant women in research including on the topic of depression during pregnancy. BabyCenter engages approximately 18 million unique users each month across the United States, ensuring more than adequate access to our proposed sample (N=600 for UPWARD and N=840 for UPWARD Supplemental Arms). Their previous longitudinal studies focused on depression during pregnancy demonstrate a proven track record in recruiting the patient population we hope to engage. BabyCenter will use two primary methods to recruit participants. A random intercept may be served to users viewing content on the BabyCenter website, with invitations targeted to specific content area, like depression or pregnancy stage. BabyCenter Community, where parents can connect with each other via chat groups organized

around pregnancy stage or topic, will also be used to recruit women meeting the inclusion criteria. BabyCenter's Community managers can post invitations to participate in a research study as a message in the relevant community boards, and women who are interested can click through to a short eligibility survey. As the majority of BabyCenter users are on mobile phones, these recruitment sources can be accessed through both desktop and mobile devices. Ineligible participants who fill out the online eligibility survey via BabyCenter will also have the option of providing their contact information to be contacted about future research opportunities either at the Center for Women's Mental Health or the University of Colorado Boulder.

IV. SUBJECT ENROLLMENT

UPWARD Study

Participants will be linked to a recruiting survey on University of Colorado Boulder's REDCap site describing the study including length, the number of assessments, and incentives, and will proceed to answer screening questions aimed at determining initial eligibility. At this point, individuals can continue with the online screening or opt out. Following identification of potential study participants, women will be given the option to either provide contact information or directly contact the research team for enrollment. Potential study participants will also be given the option of signing up for a screening call using Calendly, a secure online scheduling tool. MGH study staff trained to assess perinatal women will confirm, by phone interview, inclusion and exclusion criteria, address any questions, and review the online study fact sheet.

UPWARD and each UPWARD Supplemental Arm will have a unique study fact sheet. The online study fact sheet will accurately describe the general goals of the study and the nature of the participant's role in the study. Participants will be given the ongoing opportunity to ask any questions regarding confidentiality, participation schedule, or any other aspect of the study in the first call with the MGH team and in all subsequent contacts with study team members. After reading the study fact sheet, study staff will obtain verbal consent for participation. In addition, participants will review key points of the study with study staff, will be provided with contact information and encouragement to contact study staff members with questions via email or phone, and will be encouraged to print and retain personal copies of the study fact sheet. Consented subjects will be sent a copy of the phone consent document. This consent form will include a summary of privacy policies and date of consent. Individuals who do not provide verbal consent will be informed that it is not possible for them to participate in the study and we will provide them with a list of links to depression information websites.

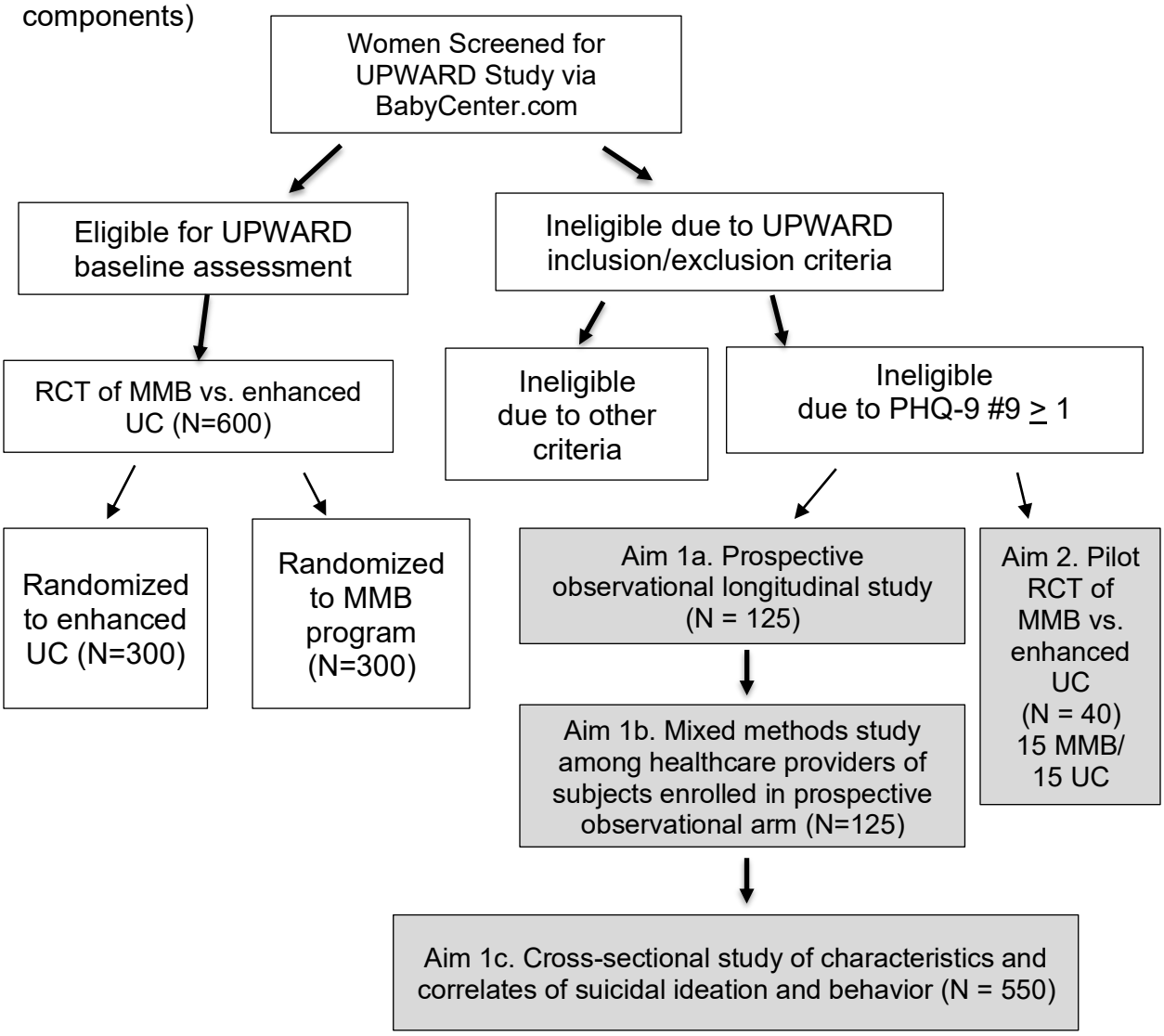
To maintain concealment, assignment will occur following the baseline assessment by telephone interview with the MGH team. Assignments will be generated using a random number table with equal probability of assignment to each group in blocks of four, which will guarantee balance for every four subjects. Randomization to study arm will be stratified based on number of prior episodes, antidepressant medication status (on medication or having discontinued at time of randomization), and baseline depressive severity based on PHQ-9 score. Women will be randomly assigned to receive MMB (n = 300) or UC (n = 300).

Study staff will also obtain contact information for community providers and consent from study participants to be in touch with these providers. This contact information will be used to send a letter describing the study and providing the consult line and availability of study doctors for questions. Additionally, we will reference the MGH Center for Women's Mental Health's website, www.womensmentalhealth.org, as a perinatal resource center that provides evidence-based safe practices for both the study participant and their clinician during pregnancy.

UPWARD Supplemental Arms

If women do not meet criteria for the UPWARD study due to suicidal ideation (PHQ-9 #9 ≥ 1), they will be recruited for prospective monitoring across the course of pregnancy and the postpartum period (n = 125) and for the proof of concept RCT (n = 40).

Figure 1. UPWARD Study Flow with Suicidality Supplement (grey background components)



For recruitment of the healthcare providers (n = 125) in UPWARD-S, we will use the same procedures implemented in the parent UPWARD study, where participation of women is contingent on providing contact information and release of information for their prenatal healthcare providers as well as an emergency contact. If the participant is currently seeing a mental health specialist, we will also ask for this provider information. If the participant does not have any additional provider, this will not constitute exclusionary criteria. Using this information, we will recruit healthcare providers and provide an online consenting process to participate in the research activities described for Supplemental Aim 1b. To recruit these providers, we will include an interest card and a business reply envelope in the mailing that is sent to providers at the time of enrollment. This interest card will prompt providers to check boxes indicating their

preference for participation in the qualitative interview, and it will have space for sharing their contact information and preferred method for being contacted. We will also include a QR code on the interest form. The QR code will link to an online version of the interest form and an online scheduling platform, which will hopefully reduce time consuming back-and-forth communication between the study teams and community providers.

Study staff will also obtain contact information for community providers and consent from study participants to be in touch with these providers in the case of psychiatric or medical emergency and for a qualitative interview discussing their provider's experience and knowledge or caring for patients expressing suicidality. Consent to contact providers will be obtained during the baseline call for UPWARD-S after the screening questions have been asked to determine eligibility and before questionnaires are administered to assess suicidal ideation. This contact information will be used to send a letter describing the study, the qualitative provider interview, and provide the consult line and availability of study doctors for questions. This letter will be sent to providers after the baseline interview with their patient. A copy of the same letter will also be sent to the participants themselves. We will reach out to providers again when participants are in their third trimester, to remind them of their patient's participation in the study, endorsement of suicidality, and availability of study doctors for questions and consults. Additionally, we will reference the MGH Center for Women's Mental Health's website, www.womensmentalhealth.org, as a perinatal resource center that provides evidence-based safe practices for both the study participant and their clinician during pregnancy.

UPWARD-Baby

Participants who were enrolled in the parent UPWARD trial will be given the opportunity to participate in the additional UPWARD-Baby timepoint. All participants who completed the UPWARD study will be sent a recruitment email between 12 and 15 months postpartum. This email will explain why participants are being contacted again and the purpose of this additional, optional timepoint. The email will direct participants to a REDCap link, which will display an online consent form with more information. After participants provide consent, the REDCap link will then direct them to the battery of UPWARD-Baby questionnaires at this 12-months postpartum timepoint (participants will have until 15 months postpartum to complete this timepoint). If participants do not complete the UPWARD-Baby surveys, study staff will reach out via text message, email, or telephone to determine if participants would like to participate in this timepoint. If participants are not interested in completing any more surveys and would not like to participate, they can choose to ignore the recruitment email and text message and not provide consent.

V. STUDY PROCEDURES

UPWARD

All procedures will be administered by telephone or electronically using secure websites. The self-report measures and behavioral tasks will be programmed and hosted by the CU Boulder site for screening, baseline assessment and follow-up data collection using REDCap (Research Electronic Data Capture[21]). Participants will be emailed secured links by the CU Boulder study team with assessment instruments that reside behind the firewall with user-limited access. All participants enter their responses using a study assigned ID, and data stored in REDCap is accessed only by the study team who must provide a user ID and password.

This study involves prospective monitoring of the study sample across their pregnancy, with self-report questionnaires completed each month and five telephone contacts with study staff for

all participants (at baseline, post-intervention, third trimester, 3 months postpartum, and 6 months postpartum). Participants will be offered the option to schedule phone interviews online via Calendly. Those who do not wish to use the online scheduling platform can choose to schedule directly with the study team via email, phone call, or text message on an encrypted study cell phone. Changes in medication and usage and dosage, as well as any relapse in depressive symptoms since the last phone contact, will be gauged during each phone call by study staff. Please see **Table 1** below for listing of assessments administered at each time point.

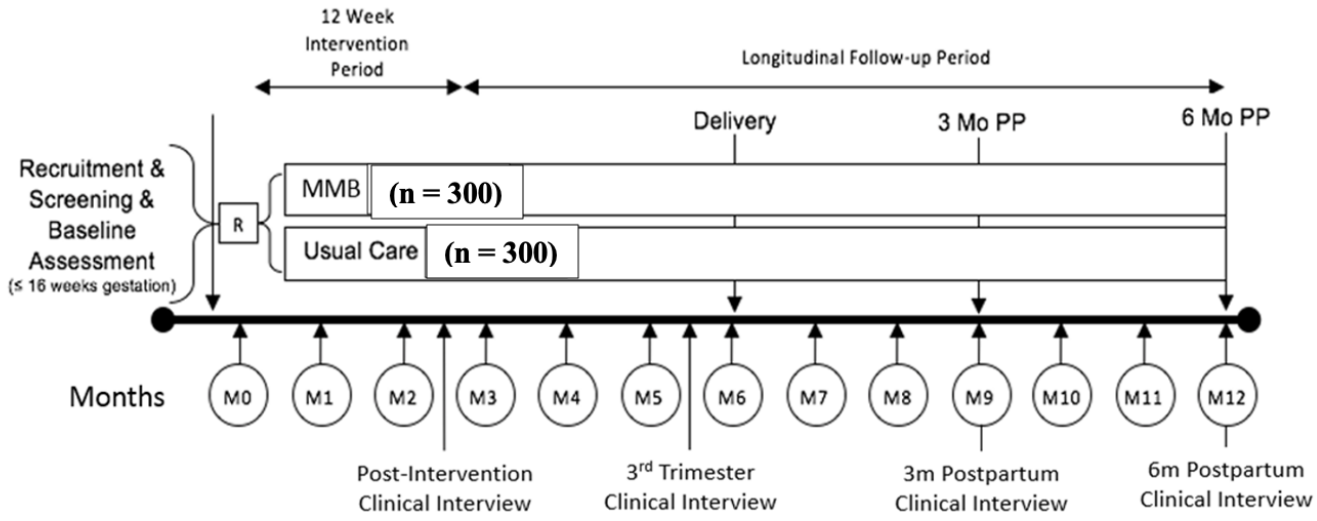


Table 1. UPWARD Measurement Schedule

UPWARD Study	Baseline	M1	W6	M2	Post-Intervention	M3	M4	M5	3T	M6	M7	M8	3PP	M10	M11	M12	6PP	12PP***
MINI full	x																	
MINI mood	x				x				x				x				x	
MADRS	x				x				x				x				x	
EPDS	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	
PHQ-8																		x
PHQ-9*	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	
CS-S**	x																	
CGI	x				x				x				x				x	
PGI	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	
GAD-7	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
PSS-10	x					x			x				x				x	x

WHODAS 2.0	x					x			x				x				x	
CSQ-8 (UC)	x					x											x	
CSQ-8 (MMB)						x												
CTQ	x																	
PROMIS	x																	
FFMQ	x		x			x												x
RRS	x		x			x												x
SCS	x		x			x												x
SSQ-SF	x					x							x				x	
RSQ-MEP	x																	
LEL	x																x	
LEIDS-R	x		x			x												
EQ	x		x			x												x
CSI	x																	x
AToM	x					x			x				x				x	
PSA	x		x			x			x									
PSQI	x					x							x				x	
Positive Mood Diary	x		x			x												x
DPES Joy Subscale	x		x			x							x				x	x
CERTS Unresolution Subscale	x																	
CERQ Acceptance Subscale	x																	
NEO-FFI Neuroticism Domain	x																	
SRET	x		x			x							x				x	x
ASQ-3													x				x	x
ASQ-SE-2													x				x	x
IBQ													x				x	x
IMP													x				x	

PSI-4-SF																		x
BITSEA																		x
PRFQ																		x
KPCS																		x
BAM-13																		x
My Baby's Day																		x
PAT																		x
CASP																		x
PANAS (post CASP; present moment instruction)																		X
ECBQ																		x

*PHQ-9 will also be administered every two weeks

** the CS-S will be conditionally delivered at any time point after PHQ-9 Q9 >0 or EPDS Q10 >0

*** only administered to participants that opt-in to do the additional 12-month assessment (UPWARD-Baby)

UPWARD Extension

The final 100 participants in the UPWARD sample of 600 individuals will participate in an abbreviated version of the UPWARD procedures. These 100 women will be recruited via the same platform of BabyCenter, screened and enrolled based on the same entry criteria, and similarly randomized to the MMB intervention or Usual Care. However, the only differences will be that these final participants in this group of 100 who are randomized to the treatment group will not receive the coaching that is typically involved in the MMB intervention. This will further investigate our research aims to assess the extent to which this modified version of MMB is still an effective means of preventing depressive relapse in a perinatal population. Moreover, these final 100 participants will not receive any follow-up clinical interviews or relapse determination calls after the initial screening and baseline calls. Participants will be randomized after the baseline call, either through a phone conversation or via email. They will instead be prospectively followed through 3 months postpartum via the same battery and schedule of self-report questionnaires given to the other UPWARD participants through this timepoint. If any participant endorses items 3, 4, or 5 on the C-SSRS via these self-report questionnaires, the same suicidality safety protocol will be triggered as outlined below. The information about the delivery and newborn outcomes that would typically be collected during the 3 months postpartum interview will now be administered as a self-report survey with the rest of the questionnaires for this timepoint.

Table 2. UPWARD Extension Measurement Schedule

UPWARD Study	Baseline	M1	W6	M2	Post-Intervention	M3	M4	M5	3T	M6	M7	M8	3PP
MINI full	x												
MINI mood	x				x				x				x
MADRS	x				x				x				x
EPDS	x	x	x	x		x	x	x	x	x	x	x	x
PHQ-9*	x	x	x	x		x	x	x	x	x	x	x	x
CS-S**	x												
CGI	x				x				x				x
PGI	x	x	x	x		x	x	x	x	x	x	x	x
GAD-7	x	x	x	x		x	x	x	x	x	x	x	x
PSS-10	x					x			x				x
WHODAS 2.0	x					x			x				x
CSQ-8 (UC)	x					x							
CSQ-8 (MMB)						x							
CTQ	x												
PROMIS	x												
FFMQ	x		x			x							
RRS	x		x			x							
SCS	x		x			x							
SSQ-SF	x					x							x
RSQ-MEP	x												
LEL	x												
LEIDS-R	x		x			x							
EQ	x		x			x							
CSI	x												
AToM	x					x			x				x
PSA	x		x			x			x				
PSQI	x					x							x
Positive Mood Diary	x		x			x							

DPES Joy Subscale	x		x			x							x
CERTS Unresolution Subscale	x												
CERQ Acceptance Subscale	x												
NEO-FFI Neuroticism Domain	x												
SRET	x		x			x							x
ASQ-3													x
ASQ-SE-2													x
IBQ													x
IMP													X
Birth experience questionnaire													x

*PHQ-9 will also be administered every two weeks

** the CS-S will be conditionally delivered at any time point after PHQ-9 Q9 >0 or EPDS Q10 >0

UPWARD-S

Just as conducted in the parent trial, all procedures will be administered by telephone or electronically using secure websites, and online data collection will be hosted and maintained by the CU REDCap and research team. Identical security and confidentiality measures will be taken in UPWARD and UPWARD-S. Participation in UPWARD-S involves prospective monitoring of the study sample across their pregnancy, with self-report questionnaires completed online every 2 weeks and five telephone contacts with study staff for all participants (at baseline, qualitative interview proximate to baseline, third trimester, 3 months postpartum, and 6 months postpartum). Participants will be offered the option to schedule phone interviews online via Calendly. Those who do not wish to use the online scheduling platform can choose to schedule directly with the study team via email, phone call, or text message on an encrypted study cell phone. Changes in or initiation of treatment, as well as any recurrence in suicidal/self-harm ideation since the last phone contact, will be gauged during each phone call by study staff. Providers of participants will be contacted for a single qualitative interview as soon as possible after enrollment of their patient in UPWARD-S. Please see **Table 2** below for listing of assessments administered at each time point for Arm 1a and **Table 3** for Arm 2.

Table 3. UPWARD-S Arm 1a Measurement Schedule

UPWARD-S	Baseline	Every 2 weeks to M3	M3	Every 2 weeks to 3rd T	3rd T	Every 2 weeks to 3 M PP	3 M PP	Every 2 weeks to 6 M PP	6 M PP
Demographic questionnaire	x								
MINI full	x								
MINI mood only					x		x		x
MADRS	x				x		x		x
CGI	x				x		x		x
EPDS	x	x	x	x	x	x	x	x	x
PHQ-9	x	x	x	x	x	x	x	x	x
CS-S	x	x	x	x	x	x	x	x	x
PGI	x	x	x	x	x	x	x	x	x
GAD-7	x	x	x	x	x	x	x	x	x
PSS-10*	x	x	x	x	x	x	x	x	x
WHODAS 2.0	x		x		x		x		x
CSQ-8 (UC)	x		x						x
CTQ	x								
PROMIS	x								
FFMQ	x		x				x		x
RRS	x		x				x		x
SCS	x		x				x		x
SSQ-SF	x		x				x		x
RSQ-MEP	x								
LEL	x								x
LEIDS-R	x		x				x		x
EQ	x		x						
CSI	x						x		x
AToM	x		x		x		x		x
PSA	x		x		x				
PSQI	x		x				x		x
ISI	x	x	x	x	x	x	x	x	x
BIS	x		x		x		x		x

BHS	x		x		x		x		x
GBS	x		x		x		x		x
PUQE-24	x		x		x				
DII	x		x		x		x		x
HHAS	x		x		x		x		x
BACQ	x		x		x		x		x
SITBI	x		x		x		x		x
CTS2	x								
DSM-5 CCSM	x		x		x		x		x
SRET and GNAT	x		x				x		x
ASQ-3							x		x
ASQ-SE-2							x		x
IBQ							x		x
Qualitative Interview	x								

* the PSS-10 will be administered once a month

Table 4. UPWARD-S Arm 2 Measurement Schedule

UPWARD Study	Baseline	Every 2 weeks to W6	W6	Every 2 weeks to M3	M3	Every 2 weeks to 3T	3T	Every 2 weeks to 3M PP	3PP	Every 2 weeks to 6M PP	6PP
Demographic questionnaire	x										
MINI full	x										
MINI mood	x				x		x		x		x
MADRS	x				x		x		x		x
EPDS	x	x	x	x	x	x	x	x	x	x	x
PHQ-9	x	x	x	x	x	x	x	x	x	x	x
C-SSRS	x	x	x	x	x	x	x	x	x	x	x
CGI	x				x		x		x		x
PGI	x	x	x	x	x	x	x	x	x	x	x

GAD-7	x	x	x	x	x	x	x	x	x	x	x
PSS-10*	x	x	x	x	x	x	x	x	x	x	x
WHODAS 2.0	x				x		x		x		x
CSQ-8 (UC)	x				x						x
CSQ-8 (MMB)					x						
CTQ	x										
PROMIS	x										
FFMQ	x		x		x				x		x
RRS	x		x		x				x		x
SCS	x		x		x				x		x
SSQ-SF	x				x				x		x
RSQ-MEP	x										
LEL	x										x
LEIDS-R	x		x		x				x		x
EQ	x		x		x						
CSI	x								x		x
AToM	x				x		x		x		x
PSA	x		x		x		x				
PSQI	x				x				x		x
ISI	x	x	x	x	x	x	x	x	x	x	x
BIS	x				x		x		x		x
BHS	x				x		x		x		x
GBS	x				x		x		x		x
PUQE-24	x				x		x				
DII	x				x		x		x		x
HHAS	x				x		x		x		x
BACQ	x				x		x		x		x
SITBI	x				x		x		x		x
CTS2	x										
DSM-5 CCSM	x				x		x		x		x
Positive Mood Diary	x		x		x						
DPES Joy Subscale	x		x		x				x		x

CERTS Unresolution Subscale	x										
CERQ Acceptance subscale	x										
NEO-FFI N Domain	x										
SRET and GNAT	x		x		x				x		x
ASQ-3									x		x
ASQ-SE-2									x		x
IBQ									x		x
IMP									x		x
Qualitative Interview	x										
Qualitative Interview (MMB)					x						

*

* the PSS-10 will be administered once a month

Table 5. UPWARD-S 550 Arm 1c (Cross-Sectional) Measurement Schedule

Measure		
Demographics		x
EPDS	Edinburgh Postpartum Depression Scale	x
PHQ-9	Patient Health Questionnaire	x
PGI	Patient Clinical Global Impression	x
GAD-7	General Anxiety Disorder-7	x
PSS-10	Perceived Stress Scale	x
WHODAS 2.0	WHO Disability Assessment Schedule 2.0	x
CSQ-8	Client Satisfaction Questionnaire	x

CTQ	Childhood Trauma Questionnaire	x
PROMIS	Patient-Reported Outcomes Measurement; Social Isolation subset	x
FFMQ	Five Facet Mindfulness Questionnaire	x
RRS	Ruminative Response Scale	x
SCS	Self-Compassion Scale	x
SSQ-SF	Social Support Questionnaire – Short Form	x
RSQ-MEP	Responses to Stress – Maternal Emotional Pregnancy Stress	x
LEL	Life Events Checklist	x
LEIDS-R	Leiden Index of Depression Sensitivity-Revised	x
EQ	Experiences Questionnaire	x
CSI	Couples Satisfaction Index	x
AToM	Attitudes Towards Motherhood Scale	x
PSA	Pregnancy Specific Anxiety	x
PSQI	Pittsburgh Sleep Quality Index	x
ISI	Insomnia Severity Inventory	x
BIS	Barrett Impulsivity Scale	x
BHS	Beck Hopelessness Inventory	x
GBS	General Belongingness Scale	x
PUQE-24	24-hour Pregnancy-Unique Quantification of Emesis	x
DII	Distress Intolerance Index	x
H2A	The Hamburg-Hannover Agitation Scale	x
BACQ	The Brief Approach/Avoidance Coping Questionnaire	x
CTS2-SF	Conflict Tactic Scale-2 Short Form	x
DSM-5 CCSM	DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure	x

DPES Joy Subscale	Dispositional Positive Emotions Scale – Joy Subscale	x
CERTS Unresolution Subscale	Cambridge Exeter Repetitive Thought Scale – Unresolution Subscale	x
CERQ Acceptance Subscale	Cognitive Emotion Regulation Questionnaire – Acceptance Subscale	x
NEO-FFI Neuroticism Domain	NEO Five-Factor Inventory Neuroticism Domain	x
GNAT	Go/No-Go Association Task	x
SRET	Self-Referent Encoding Task	x
COPE	Adapted COVID-19 Participant Experience Survey	x
CRISIS	Adapted Coronavirus Health Impact Survey	x
Adapted COVID-19 Pregnancy and Birth Questionnaire		x
EPII	Adapted Epidemic-Pandemic Impacts Inventory	x
IUS-12	Intolerance of Uncertainty Scale - Short Form	x

UPWARD Supplemental Arms

We will use the same measurement sources, data collection procedures and platforms, and data analytic methods as detailed in our parent UPWARD trial to allow further efficiencies in the conduct of the supplemental arms. We will also expand our measurement and data analytic methods in the following three ways.

First, participants in the supplemental arms will be given measurement tools that support data harmonization for domains relevant to suicidal ideation and behavior by adding PhenX Toolkit measures that are of specific relevance to the supplemental arms. Participants in the supplemental arms will also answer self-report instruments and behavioral tasks that index key social processes (e.g., belonging). For example, to measure implicit associations pairing the self with social belonging, participants will complete a Go/No-Go Task.[37] Quantitative analyses of self-report instruments and behavioral tasks will build on the methods detailed in the UPWARD parent study. **Second**, study staff will conduct qualitative interviews with both perinatal women who report suicidal ideation and behavior in the prospective longitudinal study and their health care providers. All interviews will be audio recorded and transcribed. Prior to analysis, the transcriptions will be verified and de-identified. Transcripts will be read in their entirety to confirm thematic saturation. A hierarchical coding structure will be developed using an iterative inductive-deductive approach based on the interview protocol and interview transcripts. Each code will be assigned with definitions and rules. Two separate coders will conduct an independent evaluation of each group of interviews and resolve difference by consensus. Experienced qualitative coders will establish reliability prior to coding. First established reliability in using the coding system, then independently coded the transcripts. Analysis will consist of interpreting the coded interviews and identifying higher-order themes, using an iterative inductive-deductive approach. Additionally, emails spontaneously sent from participants in the intervention group to the MMB coach may be saved on secure databases as qualitative data. Information sent in emails that would be considered important qualitative data would include participants' accounts of how COVID-19 has disrupted their life, or their experiences with the intervention. **Third**, we will obtain consent from women enrolled in the UPWARD Supplement arms to procure the obstetric and labor and delivery records.

<u>Aim 1a.</u>

Similar to the parent UPWARD Study, Aim 1a involves prospective monitoring of the study sample across their pregnancy, with self-report questionnaires completed each month and five telephone contacts with study staff for all participants (baseline, qualitative interview, third trimester, 3 months postpartum, and 6 months postpartum). Participants will first be consented before continuing with the screening process. Those determined to be ineligible after this phone screening will be dropped from the study and provided with a list of resources, including the national suicide hotline and contact information for Postpartum Support International. Consented subjects will be sent a copy of the phone consent document. This consent form will include a summary of privacy policies and date of consent. Individuals who do not provide verbal consent will be informed that it is not possible for them to participate in the study and we will provide them with a list of links to depression information websites. Participants in Arm 1 will not be assigned to the intervention and will continue with the usual care that they are already receiving from their community provider. The safety protocol will remain the same across UPWARD and all UPWARD-S. MGH physicians with perinatal psychiatry expertise will be available via a consult line for community providers of participants enrolled in UPWARD-S Arms 1 and 2. Throughout the study, they will answer questions regarding psychiatric medications and possible treatment options for individual patients determined by their community provider. Additionally, women enrolled in the supplemental arms will be asked to complete a qualitative interview with study staff during their pregnancy. The qualitative interview will be scheduled at

the time of enrollment, and participants will be asked to schedule the qualitative interview as close to their baseline enrolment interview as feasible with their schedules. The MADRS will be used at the end of the qualitative interview with perinatal women to assess suicidality and activate the safety protocol to connect participants to treatment and resources if necessary. Among women, we will probe key factors identified predictive models of suicidal risk and behavior; we will conduct open-ended interviews to assess social belonging, and we will use interview and coding procedures described in Hargus et al. (2010) to assess autobiographical memory specificity and meta-awareness.[15] We also will inquire about experiences with the healthcare system and informal support networks (e.g., reasons for reporting or not reporting suicidal ideation and behavior to providers, perceptions of what providers and the health care system could do differently, and perception of effective coping strategies during the perinatal period).

Aim 1b.

After consent to reach out to community providers in obtained in Aim 1a, a letter explaining the UPWARD Study and Supplemental Arms will be sent to the community providers overseeing the care of participants enrolled in Arm 1a. The letter will ask that these providers consider taking part in a qualitative interview with study staff. A QR code will be included in this letter that directs providers to Calendly, an online scheduling platform. This online scheduler will be securely encrypted and allow providers to select the time slot that works best for them to participate in a qualitative interview. Additionally, study staff may reach out to community providers over phone, fax, or email to recruit them for participation in the qualitative interview. Willing providers will be consented by study staff over the phone. After reading the study fact sheet, study staff will obtain verbal consent for participation. In addition, participants will review key points of the study with study staff, will be provided with contact information and encouragement to contact study staff members with questions via email or phone, and will be encouraged to print and retain personal copies of the study fact sheet. Consented healthcare providers will be sent a copy of the phone consent document. This consent form will include a summary of privacy policies and date of consent. Providers who do not provide verbal consent will be informed that it is not possible for them to participate in the study. Interviews with healthcare providers will be oriented around identifying the extent to which providers report the knowledge and skills necessary to support patients with suicidal ideation and behavior and identify areas of additional training and support needed. Queries will probe policies for supporting patients, access to mental health providers within their healthcare setting, perceptions regarding the importance of patient access to a mental health provider for comprehensive care, barriers and challenges to providing patients with care, and perceived resources for support for providers. Phone interviews with providers will be audio recorded to aid in transcription and qualitative analysis. Providers concerned about the time commitment involved in a phone interview will be asked to answer the same open-ended questions through an online REDCap survey and will be electronically consented through REDCap.

In addition to provider interviews, medical records will be requested for the 125 women enrolled in Arm 1a. As part of the enrollment process and baseline interview, all participants will be asked to sign medical record release forms giving staff permission to obtain obstetric and labor and delivery records. Medical record release forms will be sent to participants in the mail at the mailing address that they provide. A business reply envelope will be included in this mailing to facilitate returning signed forms to study staff. The requested medical records will contain relevant vital sign measures and birth outcomes, which will be reviewed by trained study staff for abstraction of outcomes. Medical records will also be used to abstract any mention or documentation suicidal ideation and how it may have been addressed in a clinical setting. We will assess the potential relationship between suicidal ideation and behavior during pregnancy and risk for adverse obstetric outcomes (e.g., preterm labor, shorter gestational age).[38] We also

will assess the extent to which prenatal healthcare providers document evidence of suicidal ideation and behavior in these records; these data will inform our description of routine care of suicidal ideation and behavior is identified and addressed in routine care across a spectrum of specialty and general practice settings. Procedures for record procurement and abstraction of relevant obstetric and neonatal data are well established based on the success of the MGH team following these procedures to obtain records from over 90% of women enrolled in the National Pregnancy Registry for Psychiatric Medications.[39]

Aim 1c.

To address Aim 1c, we will use a cross sectional design in which pregnant women who endorse suicidality with PHQ-9 item #9 scores > 1 in the UPWARD study will be asked if they are willing to consent to completing a one-time set of self-report instruments and behavioral tasks to inform our understanding of the characteristics and correlates of suicidal ideation and behavior (n = 550). Participants will read information about the study and provide consent electronically before continuing on to complete the survey battery. Consenting participants will be asked to provide a mobile phone number which will be used as an identifier to prevent duplicate survey responses from the same participant. All participants in this study also will be provided with a list of resources, including the national suicide hotline and contact information for Postpartum Support International, a well-respected group that provides local support to pregnant and postpartum women.

Aim 2.

Similar to the parent UPWARD Study and Aim 1a, Aim 2 involves prospective monitoring of the study sample across their pregnancy, with self-report questionnaires completed each month and five telephone contacts with study staff for all participants (baseline, qualitative interview, third trimester, 3 months postpartum, and 6 months postpartum). Participants will be consented prior to the initial phone screening. Those eligible will proceed to randomization and those found ineligible after the phone screening will be dropped from the study and provided with a list of resources, including the national suicide hotline and contact information for Postpartum Support International. Consented subjects will be sent a copy of the phone consent document and consented using the procedure described for the parent UPWARD study.

Participants in Arm 2 will be randomly assigned to receive MMB (*n* = 20) or UC (*n* = 20). To maintain concealment, assignment will occur following the baseline assessment by telephone interview with the MGH team. Assignments will be generated using a random number table with equal probability of assignment to each group in blocks of four, which will guarantee balance for every four subjects. Randomization to study arm will be stratified based on number of prior episodes, antidepressant medication status (on medication or having discontinued at time of randomization), and baseline depressive severity based on PHQ-9 score. The safety protocol will remain the same across UPWARD and all UPWARD Supplement arms. MGH physicians with perinatal psychiatry expertise will be available via a consult line for community providers of participants enrolled in Supplemental Arms 1 and 2. Throughout the study, they will answer questions regarding psychiatric medications and possible treatment options for individual patients determined by their community provider. As described in Aim 1a, women in the supplemental arms will be asked to participate in a qualitative interview with study staff. Women in Arm 2 will be asked to complete the qualitative interview at the time of the randomization call, or schedule the qualitative interview as close to the time of randomization call as possible. The qualitative interviews with the women who are randomized to the MMB for Moms program will follow the procedures used in Chesin et al.[35] to explore the use of MBCT among outpatients

with suicidal ideation. The MADRS will be used at the end of the qualitative interview with perinatal women to assess suicidality and activate the safety protocol to connect participants to treatment and resources if necessary. We will ask open-ended questions about women's views on the helpfulness of MMB for Moms, reasons for benefits, and difficulties. We also will inquire about women's perceptions of elements added to other MBCT protocols for specific populations, such as the use of additional introductory meetings prior to the 8-session series and the Safety Planning Intervention in the protocol for military veterans.[30]

UPWARD-Baby

All participants who were enrolled in the parent UPWARD Study and are between 12-15 months postpartum will be offered to participate in a one-time, self-report battery administered through REDCap. The purpose of this 12-months postpartum timepoint is to learn more about participants' wellness as well as their babies' development and behaviors. Eligible participants will be contacted via email to participate in the study. The email will include a REDCap link that directs participants to an online consent form followed by the battery of questionnaires. They may choose to ignore the email to opt-out of participation. If they consent and choose to move forward, they will complete the self-report questionnaires and will have up until 15 months postpartum to do so. Upon completion of these surveys, they will be sent the code to a $20 gift card. For eligible participants who do not begin the survey within two weeks of receiving it, our team will reach out to them via text to determine if they would like to be part of this additional assessment. As with the rest of the study surveys, the UPWARD-Baby survey will be sent out by the REDCap site hosted by the University of Colorado Boulder. The UPWARD-Baby timepoint will be overseen by Dr. Sherryl Goodman and her team at Emory University, which will act as a relying site for this protocol. Dr. Goodman and the Emory team will have direct access to identifiable data in the UC Boulder REDCap through their own accounts. This will allow them to contact participants for survey reminders and eventually download this data for analysis.

Baseline Clinical Assessment and Depressive Relapse

Demographic and Treatment History. Information about subjects will be gathered during the first clinical interview, including race/ethnicity, education level, and history of psychiatric treatment.

Mini-International Neuropsychiatric Interview (MINI). The MINI is a valid, structured diagnostic tool that assesses Axis I and II disorders in accordance with DSM-IV symptom criteria. The MINI will be used to establish baseline diagnoses for each participant, and to ensure eligibility criteria are met (e.g. rule out diagnoses of bipolar disorder, psychosis, or substance abuse disorder). It will also ascertain whether or not participants experienced a depressive relapse at four follow-up assessment time points. Also, participant scores $\geq$ 15 on the monthly PHQ-9 or $\geq$ 12 on the EPDS gathered remotely will prompt telephone administered relapse determination calls using the MINI. To establish initial reliability, study staff will receive training on MINI administration and will be overseen by Dr. Marlene Freeman at MGH. Evaluators will be blind to treatment condition and will meet biweekly to discuss ratings.

Depressive Symptom Burden

Montgomery-Åsberg Depression Rating Scale (MADRS): The MADRS is a widely used 10-item clinician-rated scale that describes the severity of depressive symptoms.

Edinburgh Postnatal Depression Scale (EPDS): This measure is a 10-item self-report used to measure depressive symptoms.

Patient Health Questionnaire (PHQ-9): The PHQ-9 assesses baseline depression symptom severity and depressive symptom burden.

Patient Health Questionnaire (PHQ-8): The PHQ-8 assesses baseline depression symptom severity and depressive symptom burden. It is the same as the PHQ-9 but does not include the 9th question which asks about suicidal ideation in the past seven days.

Columbia Suicide-Severity Rating Scale (CS-S): The CS-S is used to assess current suicidal ideation and behaviors at baseline and all follow-ups if endorsed on PHQ-9 #9 or EPDS #10 in the UPWARD study. The CS-S will be given at each measurement timepoint in UPWARD-S.

Clinical Global Impression Scale (CGI): The CGI comprises a study staff judgment of illness severity rated on a 7-point global severity scale.

Patient Clinical Global Impression Scale (PGI): The PGI comprises a single-item self-report of severity of illness over the past week on a 7-point likert scale.

Anxiety Symptom Burden

General Anxiety Disorder Questionnaire (GAD-7): The GAD-7 is a 7-item self-report questionnaire that assesses anxiety symptoms.

Pregnancy Specific Anxiety (PSA): The PSA is a 10-item scale to obtain information about pregnancy-specific anxiety and worries.

Perceived Stress

Perceived Stress Scale (PSS): The PSS is a 10-item self-report questionnaire that assesses the severity of recent psychosocial stressors.

Life Events List (LEL): The LEL is a 24-item scale used to assess multiple life stressors.

Functional Status

WHO Disability Assessment Schedule 2.0 (WHODAS 2.0): The WHODAS 2.0 will assess functional status.

Intervention Exposure and Satisfaction

Client Satisfaction Questionnaire (CSQ-8): The CSQ-8 is an 8-item questionnaire that will be used to assess satisfaction with digital MMB and UC.

Usual Care Characterization

To characterize the nature of UC for all participants, accurate tracking of care received, including pharmacotherapy, psychotherapy, and other interventions, will be conducted using the Treatment Tracking Sheet used in previous NIMH funded studies of perinatal depression at the MGH site. This sheet will be completed by study staff for each subject throughout their participation.

Personalization Variables

Sarason Social Support Questionnaire – Short Form (SSQ-SF): The SSQ-SF is a 12-item scale designed to assess social support.

Leiden Index of Depression Sensitivity – Revised (LEIDS-R): The LEIDS-R is a 34-item scale that measures cognitive reactivity to sad mood.

Couple Satisfaction Inventory (CSI): The CSI is a 16-item measure of partner relationship qualities.

Childhood Trauma Questionnaire (CTQ): The CTQ is a 28-item measure of childhood abuse/adversity.

Attitudes Toward Motherhood Scale (AToM): The AToM is a 12-item scale that measures women's beliefs about motherhood.

Pittsburgh Sleep Quality Index (PSQI): The PSQI is a 9-item scale that measures sleep quality.

Patient-Reported Outcomes Measurement Information System (PROMIS) Social Isolation Subset: The PROMIS social isolation 8-item short form subset is a set of 8 questions to assess perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others.

Dispositional Positive Emotion Scale (DPES): The DPES Joy Subscale is a 6-item questionnaire that measures one's dispositional tendency to feel joy in life.

Cognitive Emotion Regulation Questionnaire (CERQ): The CERQ Acceptance Subscale is a 4-item questionnaire that measures the cognitive component of emotion regulation characterized by acceptance of one's situation.

Cambridge Exeter Repetitive Thoughts Scale (CERTS): The CERTS Unresolution Subscale is a 4-item questionnaire that measures unresolved ruminative thinking styles.

NEO Five- Factor Inventory (NEO-FFI): The Neuroticism Domain of the NEO-FFI is a 12-item questionnaire that measures one's level of the personality trait of neuroticism.

Putative Targets of MMB

Five Facet Mindfulness Questionnaire (FFMQ): The FFMQ is 39-item self-report measure of domains of mindfulness (observing, describing, acting with awareness, accepting without judgment, non-reactivity).

Ruminative Response Scale (RRS): The RRS is a measure of ruminative responses to negative affect.

Self-Compassion Scale (SCS): The SCS is a 26-item measure of six constructs of self-compassion (self-kindness, self-judgement, common humanity, isolation, mindfulness, over-identification).

Experiences Questionnaire (EQ): The EQ is a 20-item measure assessing the meta-cognitive strategy of decentering, or the ability to view oneself as separate from one's emotional experience.

Positive Mood Diary: The Positive Mood Diary is a 9-item self-report questionnaire that assesses daily positive affect. It is delivered three days in a row via SMS at each measurement

timepoint, and participants respond to questions asked one at a time as a SMS text message thread.

Self-Referent Encoding Task (SRET): The SRET is a task that measures cognitive biases related to depression, in which individuals indicate whether a series of negative and positive adjectives describe themselves, and self-relevant memory biases are assessed by later asking participants to recall those words.

Parenting/ Infant Outcomes

Infant Behavior Questionnaire – Very Short Form (IBQ): The IBQ-VSF is a 37-item questionnaire for parents to report on their infant's behavior.

Interpersonal Mindfulness in Parenting (Infant) Scale (IMP): This measure represents an adaptation of the Interpersonal Mindfulness in Parenting measure (Duncan, 2007; Duncan et al. 2009) for the infant stage of development and comprises 27 items rated on a 5-point scale.

Ages & Stages Questionnaire (ASQ-3): The ASQ-3 is a screening questionnaire completed by parents, which identifies children in the age range of 1 month to 60 months, at risk of a developmental delay. The 3, 6, and 12 months of age versions of the questionnaire will be used in this study. The ASQ-3 concerns five developmental domains: Communication, Gross Motor, Fine Motor, Problem Solving and Personal Social. Next to that, open questions about the general health of the child are included and parents can indicate whether they have concerns on the development of their child.

Ages & Stages Socioemotional Questionnaire (ASQ-SE-2): This questionnaire measures socio-emotional development in seven key domains: self-regulation, cooperation, communication, adaptive functioning, autonomy, affect and interpersonal interaction. The appropriate measures for 3, 6 and 12 months of age will be used.

Brief Infant-Toddler Socio Emotional Assessment (BITSEA): This 42-item questionnaire is a well-validated screening measure for symptoms or other early signs of psychopathology, yielding scores on Externalizing, Internalizing, Dysregulation, and Competencies.

Parental Reflective Functioning Questionnaire (PRFQ): 18 items measuring mothers' capacity to think about her infant as a separate individual and understand that the baby's mental states, separate from the mother's, may drive behavior. Valid for 1-to-5-year olds.

Karitane Parenting Confidence Scale (KPCS): 15 items measuring domain-specific self-efficacy in mothers of 0- to 12-month-old infants; items ask mothers how confident they are about several parenting tasks.

Being a Mother scale (BaM-13): 13 items measuring women's feelings about motherhood in general.

The Parenting Stress Index, Fourth Edition, Short Form (PSI-4-SF): A 36-item parent-report questionnaire that screens for parenting stress. It is designed for parents of infants from birth to 12 months old.

Parenting Responsibility Scale (My Baby's Day): A set of questions based on an interview diary-based measure yielding scores on mothers' engagement with and accessibility to her baby (most recent workday and non workday)

Parenting Attributes Test (PAT): Developed to assess the perceived causes of caregiving success and failure.

The Caregiver Acute Stress Paradigm (CASP; Tronick et al., 2020): is a standardized procedure for measuring caregiving stress. Mothers watch (in randomized order) two video clips: (1) a 2-minute video clip in which they watch and hear infants crying along with a brief narrative explaining that the infants were undergoing a routine medical procedure and (s) a 2-minute video clip of infants playing and hear infant positive vocalization with a brief narrative that the infants were playing with an adult. Mothers self-rate their emotional state after each of the two episodes on a Likert scale labeled with faces, ranging from very positive affect (7) to very negative affect (1), with four being neutral and with the PANAS with "present state" instructions. The attached PowerPoint Slide shows the paradigm.

Positive Affect Negative Affect Schedule (PANAS): This brief scale is comprised of 20 items, with 10 items measuring positive affect (e.g., excited, inspired) and 10 items measuring negative affect (e.g., upset, afraid).

Early Childhood Behavior Questionnaire (ECBQ): This is a 36-item questionnaire filled out by parents used to report and describe their child's temperament, for example, noting how irritated they are or how likely they are to smile in certain scenarios.

Additional Measures - Supplemental Arms 1a and 2

Go/No-Go Task (GNAT): In the Go/No-Go Task, participants see a series of stimuli presented one at a time on a computer screen. On each block of the task they are asked to press the spacebar anytime an item from one of two categories appears. In our version, which we are using in another NIMH funded trial with depressed perinatal women, participants complete four blocks that pair me and not-me (separately) with traits of belonging (e.g., accepted, included, wanted) and rejection (e.g., isolated, abandoned, excluded).

Insomnia Severity Index (ISI): The ISI is a 9-item questionnaire that measures severity of insomnia over the past two weeks.

Beck Hopelessness Scale (BHS): The BHS is a 20-item questionnaire that measures three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations.

PUQE-24: The PUQE-24 is an assessment tool for evaluating the severity of nausea and vomiting during pregnancy (NVP). The scoring scale measures the frequency of nausea, emesis, and retching within the previous 24 hours.

DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure (DSM-5 CCSM): The DSM-5 CCSM is a 13-item self-report questionnaire that assesses mental health domains that are important across psychiatric diagnoses.

Distress Intolerance Index (DII): The DII is a 10-item self-report questionnaire about how individuals handle difficult situations and emotions.

Hamburg Hannover Agitation Scale (H2A): The HHAS is an 11 item self-report questionnaire used to measure symptoms of agitation over a one-week period.

Self-Injurious Thoughts and Behaviors Interview (SITBI): The SITBI assesses the presence, frequency, and characteristics of a wide range of self-injurious thoughts and behaviors, including suicidal ideation, suicide plans, suicide gestures, suicide attempts, and nonsuicidal self-injury

Brief Approach Avoidance Coping Questionnaire (BACQ): The BACQ is a 12-item self-report questionnaire that measures approach and avoidance styles of coping with difficult situations and problems. Items are scored on a 5-point scale.

Barratt Impulsiveness Scale SR (BIS): The BIS is a 30 item self-report questionnaire that measures impulsivity and behavioral control in the domains of motor control, non-planning, and attention.

Conflict Tactics Scale (CTS2): The CTS2 short form is a 20-item questionnaire that assesses conflicts used during partner disagreements. 10 questions are about the partner doing to the subject and 10 questions are the subject doing to the partner.

Protective Factors (deterrents) of Suicide

General Belongingness Scale (GBS): The GBS is a 12-item measure to assess a sense of general belongingness.

MMB Treatment Protocol

Participants in the UPWARD Study and UPWARD-S Arm 2 are randomly assigned to participate in MMB. The 8-session protocol for MMB is based on the theory that proposes that individuals with histories of depression are vulnerable during dysphoric states, during which maladaptive cognitive patterns present during previous episodes are reactivated and can trigger the onset of a new episode.[22] Formal and informal mindfulness practice and cognitive behavioral skills are taught to help participants cultivate mindful rather than automatic, depressogenic modes of relating to thoughts, emotions, and sensations. Additions to the standard MBCT curriculum for pregnant women are designed to increase engagement and include brief informal mindfulness, social support, and self-compassion practices as well as psychoeducation about mood and anxiety during the transition to parenthood. Our digital delivery of MBCT, called Mindful Mood Balance for Moms (MMB for Moms; see Table 2), is delivered in a mobile first digital format, which can be accessed fully from desktop or mobile devices. It is provided in an individually tailored manner that replicates the core components of the in-person MBCT program. Specifically, each session engages a sequential tripartite learning cycle that is core to the in-person MBCT program (Experiential Practice, Video-Based Vicarious Learning, and Didactic Information). This provides patients with the opportunity for threefold presentation of content, but accessed through unique and overlapping receptive learning modes.[23,24] Accompanying materials are provided for each session via digital access to forms and audio or video guides identical to those used in standard MBCT, but modified for digital delivery (e.g., presented in a more interactive format, shortened to accommodate the typical amount of text presented on screen). Participants are asked to logon to the program on a daily basis until program completion and to set a regular routine for sessions and homework practice. The digital platform

for MMB will be hosted at Brella for the study's duration. Direct access to the server is secured by a firewall with IP whitelisting and account verification. HTTPS, SSL access, and user passwords are secured with 256-bit level encryption.

The MMB for Moms program also includes social community functionality.

Finally, telephone coaching is delivered for participants to accompany the MMB for Moms digital program, consistent with the coaching manual for a 12-week intervention period. Participants may also be emailed or texted by study coaches with reminders to complete sessions or to check in about progress made. These text messages will be sent from the Google Voice platform and will be limited to information needed to schedule phone calls and not for lengthy clinical discussion. The CU Boulder site will oversee the integrity of the digital MMB condition, including telephone/text/email coaching and moderating all digital site activity, including coaching feedback and online community interactions. Participants enrolled in UPWARD Extension will receive the fully functional MMB intervention but will not receive the additional coaching component.

Data describing participant engagement with the intervention will be collected and analyzed. This includes metrics captured by the MMB platform such as the number of sessions participants complete, the number of times participants log into the platform, participants' home practice completion, and participants' reflections on mindfulness practices.

Table 2

Session number	Session topic	MMB for Moms Session Objectives
1	*Finding Your Place Beyond Blue*	Enhancing motivation for online learning; recognizing automatic patterns of reactivity associated with perpetuation of dysphoric moods; committing to mindfulness practice as a means of stepping out of automatic pilot.
2	*The Body Scan* Practice	In moving attention to specific foci in the body, contrasting intentional versus automatic deployment of attention; cognitive interpretations of interpersonal events.
3	*The Breath*	Increasing awareness of how often the mind is busy/scattered; introducing key formal practices including mindfulness of breathing, walking, and yoga.
4	*Exploring the Landscape of Depression*	Increasing awareness of the ways avoidance or clinging to particular experiences can be associated with depression; practicing a new mode of responding that stays present and attentive in the face of difficulty; identifying symptoms and cognitions characteristic of depression as early warning signs.
5	*Facing Difficulties*	Increasing use of mindful attention at the first step in responding effectively to difficulties, including difficult internal experience such as sadness; decreasing judgmental thoughts and avoidant responses to difficulties.
6	*Thoughts Are Not Facts*	Decreasing affective reactivity to thoughts previously associated with depression; learning to "de-center" from difficult thoughts, recognizing one's personal patterns of recurring thoughts,
7	*Building Your Plan of Action*	Identifying unique 'signatures' of mood worsening; identifying activities that improve or deteriorate mood; developing action

		plans to implement during periods of high risk; using mindfulness practice explicitly to guide action plan steps.
8	*Supporting Your Practice in the World*	Emphasizing the importance of regular self-care routines, identifying 'your daily routine of mindfulness practice'; reinforcing links between mindfulness practices, wellbeing and maintenance

MMB for Moms may be a promising intervention for pregnant women with suicidal ideation, as it delivers digitally both the content and structure of in-person MBCT. The standard MMB for Moms program will be implemented for participants in UPWARD Supplemental Arm 2; however, measurement expansion for Supplemental Aim 2 will probe participant responses to the content and the potential need for additional information specific to suicidal ideation and behaviors.

Usual Care (UC). Usual care will not be constrained for any study participants, including those randomized to MMB. The study will not constrain or influence women's decisions about maintenance or discontinuation of AD for all participants. Usual care will be augmented in two ways. First, we will provide ongoing study assessments and the provision of feedback to participants based on their responses to the PHQ-9, EPDS, and clinical interviews (e.g., "Your answers seem to suggest that you are having significant symptoms of depression. We recommend that you talk with your community care provider about whether treatment or modification of treatment might help"). Usual care also will be augmented by ongoing availability of study physicians with perinatal psychiatric expertise in response to queries from community providers regarding changes or reintroduction of pharmacologic treatment during pregnancy or the postpartum period for study participants.

Prospective Follow-up and Community Outreach

MGH physicians with perinatal psychiatry expertise will be available via a consult line for community providers of participants enrolled in the UPWARD Study and UPWARD-S. Throughout the study, they will answer questions regarding psychiatric medications and possible treatment options for individual patients determined by their community provider.

MGH study staff trained in interviewing techniques will administer the baseline, qualitative, post-intervention, third trimester, 3 months postpartum, and 6 months postpartum interviews completed for enrollees in UPWARD and UPWARD-S. Those enrolled in UPWARD Extension will complete only the screening and baseline calls. Participants will then be randomized either over the phone or via email. Baseline clinical instrument results will be reviewed and confirmed by study principal investigators to ensure eligibility. We will send a birth acknowledgement by regular mail, email, or both after delivery, and at periodic times during the study, we will send reminders of study engagement or gifts of nominal value to increase cohort retention.

In the UPWARD Study, in addition to regularly scheduled self-report questionnaires and phone contacts, relapse determination calls will be made to any participant scoring ≥ 15 on the monthly PHQ-9 or ≥ 12 on the EPDS. This relapse determination call will consist of study staff asking about the date of relapse and administering the MINI mood module and MADRS retrospectively to assess depressive symptoms during the time of relapse. If a depressive relapse has already been confirmed via clinical interview with the MINI mood module or the MADRS within a week of completion of self-report answers to either the PHQ-9 or EPDS, no relapse determination call will be made. However, if a depressive relapse is not documented during the clinical interview with the MINI mood module, but follow-up self-report surveys indicate increased depressive symptoms, a relapse determination call will be made.

In UPWARD, UPWARD Extension and UPWARD-S, if suicidality is endorsed with a score of greater than 1 on EPDS item #10 or PHQ-9 item #9 or on any of the self-report questionnaires (such as the SITBI or CCM), subjects will be prompted to complete the CS-S to assess risk of suicidality. Study subjects will also be given the national suicide hotline number (1-800-273-8255) and informed that answers to online questionnaires are not monitored in real time. A positive score on questions 3, 4, or 5 on the CS-S, indicating intention or plan for suicidality, will prompt a safety call by study physicians. Suicidality expressed during the course of clinical or qualitative interviews, either through discussion, endorsement of the suicidality item on the MINI mood module, endorsement of items 3, 4, or 5 on the suicidality module of the MINI, or via scoring >2 on the MADRS item 10, will prompt study staff to complete the CS-S with the participant. A positive score on items 3, 4, or 5 of the CS-S administered by staff will also prompt a safety call by study physicians. In addition, subjects will be told by study staff to call their community providers and go to their nearest emergency room. Endorsement of items 3-5 on the CS-S prompting a physician safety call has been the threshold used in previous studies at the collaborating site (University of Colorado Boulder). As this is a community-based study with collaboration from community physicians, these providers dictate treatment. We will notify community providers directly via phone or fax within 24 hours from report of positive scores on CS-S items 3-5.

VI. BIOSTATISTICAL ANALYSIS

Preliminary Analyses: Differences between the MMB and UC in demographic characteristics and depression related characteristics (e.g., symptom severity, comorbidity) will be assessed using Chi-square test for binary variables, Cochran Mantel Haenszel tests for categorical variables, and t-tests for continuous variables. Variables that show significant group differences and predict outcome will be entered in analyses as covariates; AD exposure will be included as a covariate. All participants will be considered evaluable for analysis (intent-to-treat sample). Significance levels will be evaluated at $p<.05$, and effect sizes reported.

Analysis for Specific Aim #1: To test the relative risk for depressive relapse and reduction of symptom burden between women randomized to digital MMB or UC.

For the analysis of rates of relapse, we will examine time to relapse as rated by the MINI during pregnancy and across the 6-month postpartum follow up using survival analysis. Survival rates will be compared using Cox proportional hazard regression and illustrated in Kaplan-Meier curves (Collett, 1994). However, time to attrition is a competing risk that can be related to time to relapse. We will adopt the subdistribution hazard model (SHM) developed by Fine and Gray to account for the possible non-independence of the censoring mechanism.[25]

For the continuous outcomes, we will use Hierarchical Linear Models (HLM) as our primary analytic model, which will compare change over time between groups on depressive symptom burden using the PHQ-9. HLM is flexible with respect to the nature of change over time (i.e., linear, piecewise linear, loglinear, etc.), and will accommodate the within subject correlation through the inclusion of random effects at the patient-level, accounting for the patient-to-patient deviations. Pattern-mixture models[26] will be used to assess whether important estimates (i.e., intervention effects) are dependent on missing data and to provide overall estimates of effects by averaging over the various missing-data patterns.

Analysis for Specific Aim #2: To explore the specific benefit of MMB relative to AD discontinuation and questions regarding personalization that are of strong interest to pregnant women and their healthcare providers.

H2a: Comparison of MMB to UC among women who discontinue AD: Our analysis will be the same as H1 with both the time-to relapse and continuous outcome models. We predict that rates of relapse and symptom burden among women randomized to MMB who discontinue AD will be significantly superior to those randomized to UC who discontinue AD.

H2b: Treatment Selection Algorithm: We predict that the use of a treatment selection algorithm will differentiate two profiles of women based on pre-treatment characteristics (those who are optimally suited to discontinue AD and engage MMB to minimize their risk of relapse, and those who should continue AD to minimize risk of relapse) and that women who are randomized to the algorithm indicated approach will have significantly lower risk of relapse and symptom burden than women who are randomized to their algorithm contraindicated approach.

Analysis for Specific Aim #3: To test the extent to which digital MMB engages putative targets.

To test target engagement, we will use the same HLM methods described above to compare differences between MMB and UC in change in the putative targets during the intervention period. To test target validation, we will use recent statistical developments that apply formal causal inference concepts to mediation analyses. Causal mediation approaches address violations of the assumption of sequential ignorability (e.g., no confounding/randomization of the mediator) that is required for unbiased estimates of the M (mediator) → Y (outcome) relationship. Addressing the issue of sequential ignorability yields unbiased estimates of the natural direct effect (NDE = the non-mediated effect of reduction of depressive related outcomes) and the natural indirect effect (NIE = the component of the intervention that seems to proceed through the respective mechanisms), with Total Effect = NDE + NIE.[27] A high NIE indicates that the subsequent outcomes are mediated through time-lagged mechanisms improvements. We have experience implementing these models which fall under the classification of marginal structural models (MSM), principal stratification (PS), structural nested mean models (SNMM), and rank preserving models (RPM),[28-30] which we will apply for each putative target individually. Sensitivity analyses will be implemented using approaches outlined by Ding and VanderWeele.[31]

Power Analysis for Specific Aim #1: To test the relative risk for depressive relapse and reduction of symptom burden between women randomized to digital MMB or UC.

For the analysis of rates of relapse, in our efficacy study of MBCT,[32] pregnant women who received MBCT evidenced approximately 30% lower rate of relapse than UC. In estimating the difference in relapse rates between MMB and UC, accommodating the sample size required to address Aim 2, N = 600 participants is required for randomization. With N=600, we have 95.5% power to detect a 20% difference in relapse rates (which is smaller than what we observed in our efficacy study) and allowing for 30% attrition, which is higher than attrition in our efficacy study of MBCT with pregnant women (15%) and lower than attrition in our digital delivery of MBCT work (approximately 40%).

For the continuous outcomes, using the method described by Ahn et al. to derive formulas for power estimation of linear mixed models,[33] power calculations can be made for repeated measures designs under specified assumptions. Based on a sample size of 300 per group, assuming 30% attrition for a total of 175 per arm randomized, with an alpha-level at 0.05 based on a 2-tailed test, assuming a within correlation of 0.5, we have power of 86.5% to detect an effect size of .25. Varying the effect size, we have 95.7%, 99.0%, and 99.8% power for effect sizes of 0.3, 0.35, and 0.4 respectively, which are much smaller than the d=0.70 effect size

observed in our efficacy study of MBCT with pregnant women,[34] indicating that we are sufficiently powered.

Power Analysis for Specific Aim #2: To explore the specific benefit of MMB relative to AD discontinuation and questions regarding personalization that are of strong interest to pregnant women and their healthcare providers.

H2a: Comparison of MMB to UC among women who discontinue AD: Anticipating balance across the 4 cells (randomized to MMB or UC; choice of discontinue AD or maintain AD), with approximately 300 participants across the two cells of interest, we have 82.8% power to detect a 23% difference in relapse rates with 30% attrition, which is smaller than what would be expected comparing the relapse rates among women who received MBCT (19%) in the Dimidjian et al. study of MBCT with pregnant women[32] to the rate of relapse among women who discontinued AD during pregnancy (66%) in the Cohen et al. prospective study[10]).

H2b: Treatment Selection Algorithm: Although there has been growing interest in trials focused on estimation of an optimal personalized treatment strategy,[35] there are no standard formula since the outcome of interest, the personalized treatment regimen, is not a measurable outcome as in typical power derivations.[36] Laber and colleagues provide a method for sizing such a trial, which they apply to their fertility (time to pregnancy) data example.[37] In their setting, they estimated a sample size of 280 was need to yield 80% power for superior coverage with 9 terms (including main effects and interaction terms) with an interval width of 0.38. Based on a slight modification of width to 0.40, we estimate a sample size of 250 is needed with 9 terms. Based on our prior data,[10] we project that 50% of participants randomized to MMB will discontinue AD (n=150) and 50% of participants randomized to UC will continue AD (n=150); thus, our randomized sample (N=600) should be sufficiently powered to build a model with up to 4 moderator variables (the number identified in our preliminary data). We will conduct PAI analysis with the SAS software procedure PROC QLEARN.

Power Analysis for Specific Aim #3: To test the extent to which digital MMB engages putative targets. Fritz et al. derived sample size requirements to guarantee 80% power.[38] With a small to medium effect for treatment on the mediator and a small to medium effect for treatment on outcome, covarying the mediator, the sample size for 80% power is 224 patients; therefore, our proposed sample, even with as much as 30% attrition is more than sufficient to test mediation with 80% power.

VII.. RISKS AND DISCOMFORTS

Participation in this study is not anticipated to confer risk to the fetus greater than that expected in normal day-to-day activity. Clinical studies of MBCT, including studies with non-pregnant women, have been conducted and indicate no potential risks to pregnant women or fetuses. Subject burden for participation occurs for approximately 12 months depending on gestational age at enrollment and includes the initial baseline interview, post-intervention interview, third trimester interview, 3-month postpartum interview, and 6-month postpartum interview, as well as monthly questionnaires. Participants in the UPWARD MMB condition will additionally receive telephone/email coaching through the MMB program during the 12-week intervention period. However, participants in UPWARD Extension will not complete any prospective clinical interviews beyond the baseline call, and will only be followed longitudinally through self-report surveys through 3 months postpartum. There are no known psychological, social, economic or legal risks for participation or completing the questionnaires or interviews. However, it is possible that participants may experience temporary and mild psychological discomfort as a result of thinking about painful aspects about their lives and relationships with others as a result

of survey questions. For instance, examples of the most personal and sensitive questions include asking about abuse of alcohol or illegal drugs and history of suicidality. The topics in the MMB program may evoke painful or uncomfortable feelings (e.g., when directing attention to self-critical thoughts); however, these risks are no greater than what would occur in daily life. Patients will be advised that all questions are voluntary.

We will include detailed information about possible risks in the study fact sheets, which illustrate the most sensitive types of questions about which subjects will be asked on the questionnaires and as part of the MMB intervention, should they be randomized to that condition. Participants also will be instructed that they may discontinue participation in the study or the MMB intervention, and/or choose not to complete web-based assessments at any time by informing the research team by phone or email.

It is possible that participants may experience injury or discomfort when engaging in the mindfulness stretching/yoga practices at home. The mindfulness and yoga practices included in the MMB intervention have been specifically tailored to pregnant and postpartum women. A description of the mindfulness/yoga components will be included in the consent form so that individuals are informed about the nature of the practices, and the digital program will instruct participants not to engage in any exercise or practice they think will be harmful to their health or well-being.

Usual care will not be constrained for any study participants, including those randomized to MMB. Usual care will be augmented by ongoing study assessments and the provision of feedback to participants based on their responses to the PHQ-9, EPDS, and clinical interviews (e.g., “Your answers suggest that you are having significant symptoms of depression. We recommend that you talk with your prenatal care provider about whether treatment might help”). Usual care also will be augmented by ongoing availability of study physicians with perinatal psychiatric expertise for community clinicians treating women with pharmacologic treatment. All treatment decisions, including use of medications and treatment of emergent symptoms, will be managed by the participant’s community prescriber who is not a study investigator. Participants in the UC group will be followed naturalistically, and no clinical interventions will be made by study investigators. The probability and magnitude of harm or discomfort associated with participation in this arm of the study is not anticipated to be greater than that encountered in daily life.

Participants also may feel inconvenienced by the time required to complete the research procedures. Participants will be informed about the expected duration of each assessment time point and MMB practice sessions for participants in that arm, and we have designed the assessment procedures to minimize burden on participants. Participants in the parent UPWARD Study will receive a total of $175 for completing the study assessments in compensation for their participation. Those who choose to complete the UPWARD Baby timepoint at 12 months postpartum will be compensated an additional $20. Participants in UPWARD Extension will receive a total of $140 for completing the study assessments. Participants in UPWARD Supplement Arms 1a and 2 will be compensated $200 for their participation in the study ($25 more than parent UPWARD study to compensate for participation in qualitative interviews and additional self-report questionnaires). Providers that participate in UPWARD Supplement Arm 1b will be compensated $75 for their participation in the qualitative interview. Participants in UPWARD Supplemental Arm 1c will be compensated $25 for completing the online survey, which will be texted to them as a gift card code on the mobile phone number they provide at consent. Participants assigned to the MMB condition also will receive the intervention at no cost. Participants who terminate participation early will be paid a prorated amount depending on the

length of their participation, and if participation in the study is ended by the investigator, participants will receive a prorated amount depending on the length of their participation.

Subjects who have a history of depression will be included in the proposed trial and therefore the recurrence or exacerbation of mood symptoms during study participation is a possible but expected risk. Suicidal ideation reported in phone interviews or self-report questionnaires over the course of study will be addressed in a timely manner by study staff who can refer to the community provider or emergency services. Specifically, we will carefully monitor depressive symptoms, including suicidality, throughout the study, using the PHQ-9[39] and EPDS completed at regular assessment points via REDCap, and on the real-time phone contacts and interviews administered by MGH study staff, which assess depression course and relapse.

If a participant scores greater than or equal to 15 on the PHQ-9 or greater than or equal to 12 on the EPDS, the online data collection and management system (REDCap) will automatically provide participants with contact information for national mental health crisis resources and for the research study team. Study investigators will be notified immediately via an algorithm programmed into REDCap. In the UPWARD parent trial and UPWARD-S Arms 1a and 2, study staff at MGH will initiate a clinical response by phone call to assess clinical status and suicidality as soon as possible within 24 business hours of report. The score of 15 is suggested as the threshold for moderate depression.[39] Additionally, we will monitor specifically responses to the suicide item (#9) on the PHQ-9: 'Thoughts that you would be better off dead or hurting yourself in some way.' and the suicide item (#10) on the EPDS: 'The thought of harming myself has occurred to me' for all study participants. If a participant endorses either of these items with a score of 1 or greater, REDCap will automatically route participants to fill out the Columbia Suicide Severity Rating Scale (CS-S) and provide participants with contact information for national mental health crisis resources and for the research study team. Study investigators and staff will be automatically notified by the REDCap system for a positive score on questions 3-5 of the CS-S in order to provide outreach as soon as possible within 24 hours and assessment of the patient by a study doctor. In UPWARD-S, endorsement of current suicidal ideation on the SITBI or CCM item (#11) will also automatically route participants to fill out the CS-S. Any endorsement of items 1-5 of the CS-S will prompt administration of the full CS-S to capture duration and intensity of suicidal ideation and/or behaviors. Furthermore, any participant who misses a scheduled assessment point will be contacted immediately by study staff. Study staff will continue to try to reach participants until a participant indicates that they no longer wish to be contacted or the participant has reached six months postpartum by their estimated date of delivery, whichever comes first. Throughout the study, all participants also will be encouraged to contact the study staff at the first sign of increased depression.

During the telephone-based assessments, MMB coaching calls, or other telephone contacts, study staff are provided ongoing education and supervision in the event of potential clinical problems and are instructed to have a very low threshold for obtaining consultation. Endorsement of suicidality will initiate a protocol used in other studies by the MGH and UCB teams where the study physician will reach the patient, assess suicidality, and refer to the community prescriber or provider and/or to emergency services, based on participant interview. Drs. Dimidjian and Cohen carry cell phones listed with all study staff to provide immediate clinical supervision if needed. If a participant expresses non-emergent mental health needs, research staff will encourage them to contact their community prescriber or provider. If over the course of the phone contact the caller becomes emotionally distressed, is not making clear sense, sounds intoxicated or impaired, or expresses thoughts of suicide or homicide, study staff will inform the participant that a study doctor will call them back as soon as possible within a few hours. At that point, the study investigator will guide the interview to ascertain the acuity and/or

potential for harm. The study investigator will first determine if the caller is alone or has access to another adult capable of transportation. If the study investigator determines that the participant is in need of emergent care, the options for such care will be discussed with the caller and may include referral to the closest emergency room, or notification of emergency services for transportation to ER, and the participant's emergency contact and community prescriber or provider will be notified.

In the parent UPWARD Study and UPWARD Extension, procedures for responding to suicidal ideation are put into play as needed during the course of prospective monitoring, and these will be expanded for the Supplement Arms. Specifically, they will be initiated at the time of study enrollment when subjects are determined to be otherwise eligible for study inclusion. Participants endorsing suicidality via PHQ-9 #9 > 1 during the screening process will complete a self-report version of the Columbia Suicide Severity Rating Scale (CSSRS). Any positive endorsement of items 3-5 on the CSSRS at the time of enrollment, indicating intent or plan, will immediately trigger notification of study clinicians to initiate outreach procedures to the participant and to community provider or emergency contact. Suicidality expressed during the course of clinical and qualitative interviews, either through discussion, endorsement of suicidality on the MINI mood module, endorsement of items 3, 4, or 5 on the suicidality module of the MINI, or via scoring >2 on the MADRS item 10, will prompt study staff to complete the CS-S with the participant. A positive score on items 3, 4, or 5 of the CS-S administered by staff will also prompt a safety call by study physicians. In addition, subjects will be told by study staff to call their community providers and go to their nearest emergency room. During this risk assessment, study doctors will assess risk and recent symptoms by completing the full version of the CSSRS, collecting information about ideation, intensity of ideation, and suicidal behaviors. Outcome of this assessment will be shared with community providers.

At the time of subject enrollment for the UPWARD Supplemental Arms, participants will be notified of the outreach to their community providers during the informed consent process. Following enrollment, community providers will be sent a letter notifying them of their patient's enrollment in the study and endorsement of suicidal ideation. Aside from the information that is shared during safety outreach to community providers in the parent UPWARD study (patient name, specifics of expressing suicidal ideation - i.e. questions endorsed through self-report questionnaire, date of endorsement), no additional data collected from participants will be shared at the time of initial outreach to community providers or during the qualitative interviews with providers described in Supplemental Aim 1b. During physician safety calls, any information necessary to ensure participant safety (as determined by the study psychiatrist making the phone call) will be shared with their community provider.

Endorsement of items 3-5 on the CS-S prompting a physician safety call has been the threshold used in previous studies at the collaborating site (University of Colorado Boulder). As this is a community-based study with collaboration from community physicians, these providers dictate treatment. As noted above, consent to communicate with these individuals is obtained as a required part of enrollment in the parent grant and will be applied in the supplement. The feasibility of establishing close communication with community-based providers of pregnant women with depression with and without suicidality enrolled in prospective studies is well established from previous federally funded grants conducted by the MGH group over the last 15 years as well as with the randomized participants already enrolled in the parent UPWARD grant. We have also engaged a national leader in the investigation of suicide, Dr. Maria Oquendo (an expert in suicide research and a co-creator of the CSSRS) as a consultant to advise us on the other ways in which the clinical assessment of suicidality may be refined particularly with respect to evaluation of pregnant and postpartum women.

In another potential scenario not directly related to assessment of suicidality but relevant to prospective follow-up, queries may arise from participants' community prescriber or provider regarding changes or reintroduction of pharmacologic treatment during pregnancy or the postpartum period. In this situation, study physicians with expertise in perinatal psychiatry will be available to provide consultation to these providers. This procedure of support to community prescribers has been successfully used by the MGH team across multiple studies in which participants were prospectively followed with standardized instruments during pregnancy and the postpartum period while concurrently followed clinically by community-based prescribers.

There are risks to confidentiality and privacy associated with participation in all research studies and in studies of digital interventions. A number of steps have been taken to safeguard privacy and confidentiality across the study. All study staff will be required to sign statements indicating that they understand confidentiality and agree to protect against risk of confidentiality. Study personnel and materials will assure that participants understand the confidentiality measures taken in this study to protect them and their information. Participants will be invited at any time to share their concerns with the study staff, investigators, or IRB representatives.

Also, participating in this study will involve access to four websites: the MMB website – where the 8-session program will be presented, Qualtrics – where the SRET data and GNAT will be collected, the REDCap website – where the online surveys will be completed, and Calendly to facilitate scheduling. The digital platform for MMB will be hosted at Brella for the study's duration. Direct access to the server is secured by a firewall with IP whitelisting and account verification. HTTPS, SSL access, and user passwords are secured with 256-bit level encryption. Passwords and their associated web access will be deleted from the study registry by study staff at the close of this study or at the participant's termination or completion of the study, whichever is earlier. The study team will have administrative access to the website. Brella is experienced in managing confidential data using encryption and passwords. Calendly uses a secure server and data center accredited under: ISO 27001, SOC 1 and SOC 2/SSAE 16/ISAE 3402 (Previously SAS 70 Type II), PCI Level 1, FISMA Moderate and Sarbanes-Oxley (SOX). Scheduling information that passes through Calendly is encrypted, both in transit and at rest. All connections from the browser to the Calendly platform are encrypted in transit using TLS SHA-256 with RSA Encryption.

Study data will be collected and managed using REDCap. REDCap is a secure web application designed to support data capture for research studies. The database is hosted at the University of Colorado Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. This project uses REDCap Twilio integrated functionality to allow participants to respond via SMS text message to the questions asked in the positive mood diary. A REDCap and Twilio account are linked together. When a user indicates that an SMS (text) or a call should be sent to a cell phone, REDCap requests that action through Twilio. When a user responds, Twilio relays that information back to REDCap. The data is stored in the REDCap database. Twilio does not store any data nor does it keep a log of its actions. All voice calls and SMS messages will be routed through Twilio's servers, but REDCap goes to great length to ensure that voice call records and SMS transcriptions do not stay in Twilio's logs but are removed shortly after being completed. This is done for security and privacy concerns (e.g., HIPAA), in which participants' phone numbers and their survey responses do not get permanently logged on Twilio's servers but instead remain securely in REDCap.

Another risk to confidentiality involves unauthorized access to a participant's login information if that information is inadvertently left in plain view. Although this risk is not completely preventable, we will instruct participants in the importance of keeping their login information secure and confidential.

The digital MMB program makes available an online community; however, this will be moderated by the research team in order to maximize anonymity. Though unlikely in the context of national recruitment, it is possible that individuals may identify one another despite such efforts and not protect the privacy of other members. We will inform participants of this potential in the consent form, and we will also explicitly ask participants in the process of seeking consent to maintain the privacy of all participants.

We anticipate that the additional 12-months postpartum timepoint (UPWARD-Baby) will not present any additional risk for participants compared to that of the parent study. Because we are asking the PHQ-8 at this timepoint instead of the PHQ-9 (which is what is asked throughout the parent study), we will not learn about suicidal ideation and therefore a safety plan for SI is not needed.

VIII. POTENTIAL BENEFITS

Participants may benefit from ongoing clinical monitoring of depressive symptoms and, in all arms except UPWARD Extension, provision of feedback. In addition, participants assigned to the MMB condition may experience an increase in knowledge about depression and how to decrease future risk for relapse. All participants enrolled in the study will have any benefits afforded by the assessment protocol with respect to the possible early identification of depressive symptom exacerbation and information about accessing national mental health services and potential consultation to their community prescriber. Since contact with the study team will occur at multiple time points, subjects will have the opportunity to easily access experts in the area of depression and pregnancy.

Lastly, subjects will be compensated for their participation. Participants in the parent UPWARD Study will be compensated $175 for their participation in the study. Participants in UPWARD Extension will be compensated a total of $140 for their participation in the study. Participants in UPWARD Supplement Arms 1a and 2 will be compensated $200 for their participation in the study ($25 more than parent UPWARD study to compensate for participation in qualitative interviews and additional self-report questionnaires). Providers that participate in UPWARD Supplement Arm 1b will be compensated $75 for their participation in the qualitative interview.

Study physicians with expertise in perinatal psychiatry will be available as a resource to community providers for advice and management of participants' clinical care. If questions arise regarding changes or reintroduction of pharmacologic treatment during pregnancy or the postpartum period, study physicians can provide consultations to these providers, thus spreading clinical knowledge and equipping providers with the tools to provide evidence-driven care.

Recent reviews have called for additional research examining mindfulness-based interventions among adults with suicidal ideation and behavior.[26] These recommendations are based, in part, on studies of mindfulness-based cognitive therapy (MBCT) among adults with histories of suicidal ideation and behavior.[16,27-29] Clinical trials in progress are examining the extension of MBCT for specific populations with suicidal ideation, such as veterans[30] and young adults.[31]

Additionally, some evidence suggests specific processes by which these benefits may be conferred in MBCT, such as meta-awareness, specificity of autobiographical memory,[15,16] the strengths of association between depression symptoms and suicidal thoughts,[32] and asymmetry in resting EEG activation.[33] Given this evidence, MMB for Moms may be a promising intervention for pregnant women with suicidal ideation, as it delivers digitally both the content and structure of in-person MBCT. That said, there is also good justification for taking an incremental approach to the use of MMB for Moms with this population.

IX. MONITORING AND QUALITY ASSURANCE

Dr. Dimidjian and Dr. Cohen will co-monitor ongoing safety of study participants. They will provide training to study staff at each site to ensure that all study staff are prepared to implement safety protocols and to identify and review immediately with the study investigators any risk to the safety, privacy, or confidentiality of participants, any problems with data collection or management, or deviations from the protocol. Furthermore, they will be trained in specific protocols in place for study to staff to report any adverse events to the study investigators. Research coordinators will meet twice weekly with the study PIs to review any safety concerns, and there will be weekly project management calls with the PIs and study research coordinators at both sites. Study binders and databases will be reviewed on a continuing basis to monitor accuracy and completion.

A Data Safety Monitoring Board (DSMB) will be established for trial monitoring. The DSMB will consist of four persons, including a psychiatrist with expertise in depression care management, a psychologist with expertise in the design and implementation of pragmatic clinical trials, a Ph.D.-level statistician, and an expert in online intervention or education delivery. None of these persons will be involved directly in the study. The DSMB has agreed to oversee the UPWARD Study and UPWARD-S components. The DSMB will have the following aims:

- To assure the safety, privacy, and confidentiality of human subjects
- To assure the reliability, validity, completeness, and integrity of the data collection, entry, and management process
- To review implementation of the human subjects protocol, including all proposed protocol amendments and modifications
- To review all serious adverse events, less serious adverse events, rates of dropout or study withdrawal, and rates of missing data

The DSMB will have a minimum of two teleconferences per year for the study duration. Members will also meet via email as needed and by teleconference call if serious adverse events attributable to study procedures are reported. Prior to its regular meetings, the study team will prepare reports to the DSMB about progress toward achieving the scientific aims, including study enrollment and patient flow, dropout and retention, data quality, confidentiality, and safety issues. The DSMB also will be provided with blinded reports of intervention effectiveness to inform judgments about the value of interim analyses. Both Dr. Dimidjian and Dr. Cohen will attend all meetings with the DSMB.

The DSMB will issue independent reports to the IRBs and the NIMH summarizing its review of these domains. If the DSMB believes that participants are being endangered, the Board will make recommendations to the NIMH and IRBs as to whether the trial should be stopped or procedures modified. If indicated, the independent reports from the DSMB will suggest ways to reduce risk and improve the quality of care of participants, and ways to improve the reliability, validity, integrity, and confidentiality of the data collection procedures.

An advisory stakeholder panel, composed of prior collaborators and women with perinatal mood and anxiety disorders, will be established to provide advice on study procedures and discuss participation burdens and ease of use. This group will function solely in an advisory capacity, and will not view protected health information, data, or research subject-specific information. We will use this panel to review procedures and various protocols prior to enrollment of subjects to ensure they are reasonable for subject participation.

All participants, regardless of treatment condition to which they have been randomized, will receive one telephone contact per trimester by MGH study staff, who will administer the mood module of the Mini International Neuropsychiatric Interview (MINI)[40]and who will be blind to randomized condition. Phone interviews will be audio recorded for supervision and data quality insurance purposes. These recordings will help the research team understand how the intervention works and maintain consistency across interviewers. Like all research information, these recordings will be stored on a secure server and kept confidential. All audio files will be labeled with an assigned study code number and will be used for research and teaching purposes only. Audio files will be stored on secure, password protected servers, accessible only to key study personnel.

Research staff will receive intensive training prior to conducting assessments with study participants. Training will include orientation to the MINI, observation of live training interviews, and co-rating of training interviews. Interviewers will need to establish interrater reliability (weighted kappa statistic) > .80 before interviewing study participants. Formal supervision of the interviewers and the reliability process will be provided by Dr. Marlene Freeman at MGH.

During the course of the protocol, study and non-study related events such as hospitalization or recurrence of depression may occur; our risk management protocols are in place to address these events as they occur. All study staff are trained and available to manage adverse events. Physicians are available by phone and pager to be informed of serious adverse events. Study investigators will report adverse events to the IRB following the PHRC guidelines, including reporting within 5 business days. Investigators will also report the event to the DSMB, including the details of the event, the severity of any reactions, the phase of the study, and the procedures for its resolution. In addition, the study investigators will ensure that the NIMH Program Officer is informed of any actions taken by the IRB as a result of such events.

These events will be promptly reported to the MGH IRB, according to the Code of Federal Regulations, and the subject's primary care and mental health providers will be informed with the subject's permission.

X. REFERENCES

1. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. *The Lancet.* 2014;384(9956):1800-1819.

2. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. *JAMA psychiatry.* 2016;73(8):826-837.
3. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry.* 2010;67(10):1012-1024.
4. Goodman SH, Tully EC. Recurrence of depression during pregnancy: Psychosocial and personal functioning correlates. *Depression and anxiety.* 2009;26(6):557-567.
5. Di Florio A, Forty L, Gordon-Smith K, et al. Perinatal episodes across the mood disorder spectrum. *JAMA psychiatry.* 2013;70(2):168-175.
6. Cohen LS, Nonacs R. Neurodevelopmental Implications of Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Untreated Maternal Depression: Weighing Relative Risks. *JAMA psychiatry.* 2016;73(11):1170-1172.
7. Wisner KL, Zarin DA, Holmboe ES, et al. Risk-benefit decision making for treatment of depression during pregnancy. *Am J Psychiatry.* 2000;157(12):1933-1940.
8. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry.* 2009;31(5):403-413.
9. Patel SR, Wisner KL. Decision making for depression treatment during pregnancy and the postpartum period. *Depression and anxiety.* 2011;28(7):589-595.
10. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *Jama.* 2006;295(5):499-507.
11. Roca A, Imaz ML, Torres A, et al. Unplanned pregnancy and discontinuation of SSRIs in pregnant women with previously treated affective disorder. *J Affect Disord.* 2013;150(3):807-813.
12. Murray L. Postpartum depression and child development. *Psychological Medicine.* 1997;27:253-260.
13. Beck C. The effects of postpartum depression on child development: A meta-analysis. *Achives of Psychiatric Nursing.* 1998;12(1):12-20.
14. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. Staying well during pregnancy and the postpartum: A pilot randomized trial of mindfulness-based cognitive therapy for the prevention of depressive relapse/recurrence. *Journal of consulting and clinical psychology.* 2016;84(2):134.
15. Dimidjian S, Beck A, Felder JN, Boggs JM, Gallop R, Segal ZV. Web-based mindfulness-based cognitive therapy for reducing residual depressive symptoms: an open trial and quasi-experimental comparison to propensity score matched controls. *Behaviour research and therapy.* 2014;63:83-89.
16. Felder JN, Segal Z, Beck A, et al. An open trial of web-based mindfulness-based cognitive therapy for perinatal women at risk for depressive relapse. *Cognitive and behavioral practice.* 2017;24(1):26-37.
17. Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. *Arch Gen Psychiatry.*67(12):1256-1264.
18. Williams JMG, Crane C, Barnhofer T, et al. Mindfulness-based cognitive therapy for preventing relapse in recurrent depression: a randomized dismantling trial. *Journal of consulting and clinical psychology.* 2014;82(2):275.
19. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *The Lancet.* 2015;386(9988):63-73.

20. DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. *PloS one.* 2014;9(1):e83875.
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
22. Segal ZV, Williams JMG, Teasdale JD. *Mindfulness-Based Cognitive Therapy for Depression: A New Approach to Preventing Relapse.* New York City, NY: Guilford Publications; 2002.
23. Eastmond DV. Adult learners and internet-based distance education. *New Directions for Adult and Continuing Education.* 1998;78:33-41.
24. Dirkx JM. The meaning and role of emotions in adult learning. *New Directions for Adult and Continuing Education.* 2008;2008(120):7-18.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association.* 1999;94(446):496-509.
26. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods.* 1997;2(1):64-78.
27. VanderWeele TJ. *Explanation in causal inference: Methods for mediation and interaction.* New York: New York: Oxford University Press; (2015). .
28. Have TR, Joffe MM, Lynch KG, Brown GK, Maisto SA, Beck AT. Causal mediation analyses with rank preserving models. *Biometrics.* 2007;63(3):926-934.
29. Lynch KG, Cary M, Gallop R, Ten Have TR. Causal Mediation Analyses for Randomized Trials. *Health services & outcomes research methodology.* 2008;8(2):57-76.
30. Gallop R, Small DS, Lin JY, Elliott MR, Joffe M, Ten Have TR. Mediation analysis with principal stratification. *Stat Med.* 2009;28(7):1108-1130.
31. Ding P, Vanderweele TJ. Sharp sensitivity bounds for mediation under unmeasured mediator-outcome confounding. *Biometrika.* 2016;103(2):483-490.
32. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. Staying well during pregnancy and the postpartum: A pilot randomized trial of mindfulness-based cognitive therapy for the prevention of depressive relapse/recurrence. *J Consult Clin Psychol.* 2015.
33. Ahn C, Overall JE, Tonidandel S. Sample size and power calculations in repeated measurement analysis. *Comput Methods Programs Biomed.* 2001;64:121-124.
34. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. Staying well during pregnancy and the postpartum: A pilot randomized trial of mindfulness-based cognitive therapy for the prevention of depressive relapse/recurrence. *J Consult Clin Psychol.* 2016;84(2):134-145.
35. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med.* 2010;363(4):301-304.
36. Laber EB, Lizotte DJ, Qian M, Pelham WE, Murphy SA. Dynamic treatment regimes: Technical challenges and applications. *Electronic Journal of Statistics.* 2014;8(1):1225-1272.
37. Laber EB, Zhao YQ, Regh T, et al. Using pilot data to size a two-arm randomized trial to find a nearly optimal personalized treatment strategy. *Stat Med.* 2016;35(8):1245-1256.
38. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. *Psychol Sci.* 2007;18(3):233-239.
39. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16:606-613.

40. Lecrubier Y, Sheehan DV, Weiller E, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *Eur Psychiatry.* 1997;12(5):224-231.