A. SIGNIFICANCE

A.1. Perinatal depression is an important public health problem that poses difficult treatment decisions for pregnant women and their healthcare providers. Perinatal depression is prevalent, estimated at 12% to 22%, [1-4] and it is associated with increased risk of adverse obstetrical and neonatal outcomes, including shorter gestational age, increased rates of preterm delivery and low birthweight, and affective and behavioral dysregulation during childhood. [5-7] Pregnant women with a history of depression are at even greater risk of relapse during the perinatal period, estimated at 30-40%. [8, 9]

Antidepressants (ADs) are the most common treatment for perinatal depression and prescribing rates during pregnancy are increasing, [10] yet a majority of women prefer non-pharmacologic treatments over ADs [11-16] because of concern about the risks of fetal exposure [17-20] and potential adverse outcomes for their infants. [13, 18, 21, 22] Moreover, over two-thirds of women who discontinue ADs in pregnancy relapse. [23] Absent non-pharmacologic relapse prevention options, women must weigh the increased risk of relapse from discontinuing ADs during pregnancy (and subsequent adverse outcomes for their infants) against the risk of adverse infant outcomes associated with fetal AD exposure. [24, 25] These difficult treatment decisions are unique to pregnant women compared to the general population of adults with depression and they highlight the critical need for effective non-pharmacologic preventive treatments. Reviewing this evidence, the US Preventive Services Task Force now recommends psychotherapy to prevent depression relapse in pregnancy [26, 27].

A.2. Mindfulness-based cognitive therapy (MBCT) is an effective non-pharmacologic preventive treatment that targets the precursors to depressive relapse. MBCT is an eight-session in-person group intervention targeting risk factors for depressive relapse through a combination of mindfulness meditation and cognitive-behavioral strategies. The theory underlying MBCT is that patients with recurrent depression are vulnerable to ruminative and self-critical cognitive patterns that increase their risk for relapse. [28-32] MBCT targets these habitual "automatic" dysfunctional cognitive patterns, training individuals to disengage from them and to develop non-judgmental openness and curiosity about inner experience. [33]

A substantial evidence base supports the effectiveness of MBCT. A meta-analysis of 9 randomized trials of MBCT involving 1,258 participants showed a 31% reduction in depressive relapse risk compared to controls over a 60-week follow-up period. [29] Results from our randomized trial of MBCT adapted for pregnant women demonstrated a 31.8% reduction in postpartum relapse risk (see **C.1.1**). Digitally-delivered MBCT has also been shown to significantly reduce depression severity and to target precursors to depressive relapse, including reducing rumination, and increasing mindfulness (see **C.1.2**). [34] Evidence that MBCT engages targets of rumination and mindfulness that mediate relapse risk is also provided by neuroscience studies. [35]

A.3. Digitally-delivered MBCT adapted for pregnant women has potential to overcome barriers to broader dissemination in healthcare systems. In-person MBCT (or any in-person treatment) for pregnant women faces several impediments to broader dissemination in healthcare systems, including logistical challenges of securing space for groups and scheduling patients, a shortage of clinicians trained to deliver MBCT with fidelity, service costs, and travel time to clinics, especially for women with limited transportation options and child care responsibilities. In response to these challenges, Dimidjian, Segal, and Goodman developed a mobile-first digital platform for MBCT tailored to pregnant women, Mindful Mood Balance for Moms (MMBFM). Initial testing of MMBFM has shown feasibility, acceptability, and effectiveness (see **C.1.1** and **C.1.2**). Evaluating effectiveness and scalability of MMBFM in a larger population is a critical next step. [36] To accomplish this, we propose to use the Accelerated Creation-to-Sustainment (ACTS) model for technology-enabled service (TES) [37] as a framework to guide our implementation efforts, and a hybrid type II effectiveness-implementation trial design using the RE-AIM model [38] to evaluate implementation outcomes.

B. INNOVATION

This proposed project has the several Innovative features: 1) MMBFM is a mobile-first digital mental health intervention, augmented with telephonic and digital coaching support, and scalable for larger populations while maintaining fidelity to the core components of MBCT. It was designed to provide pregnant women at risk for depression with expanded access to an evidence-based non-pharmacologic prevention intervention; 2) MMBFM was developed with significant input from both OB providers and patient stakeholders with lived experience of perinatal depression. It addresses the unique concerns of pregnant women at risk for depression, including video-based vicarious learning featuring a diverse group of pregnant women, and psychoeducation about mood and anxiety during the transition to parenthood. In addition, MMBFM aligns well with pregnant women's high usage of the internet for pregnancy-related information [39]; 3) The MHRN data infrastructure enables us to conduct a pragmatic effectiveness trial and a large-scale implementation study

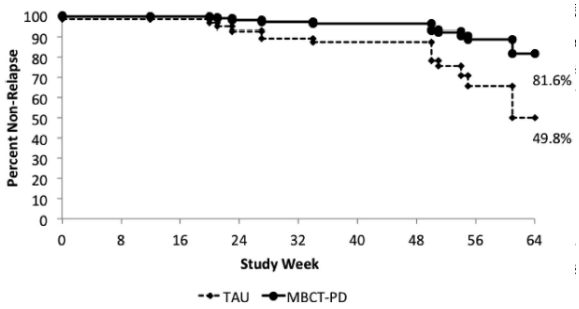
efficiently, using comprehensive records data to identify and outreach target populations in near real-time, recruit and enroll participants via secure patient portals, email, or mail, use online consent, and use web-based surveys for outcome assessment. As members of the Healthcare Systems Research Network, participating sites have the shared capability of linking maternal and infant records, allowing for efficient yet comprehensive assessment of perinatal and neonatal outcomes; 4) The hybrid type II effectiveness-implementation design using MHRN data infrastructure and technologies, will provide important data on effectiveness (putative targets of MMBFM, outcome data for women and their infants), as well as implementation (factors that facilitate or impede scale-up of MMBFM).

C. APPROACH

C.1. Preliminary studies

C.1.1. Efficacy of MBCT in reducing depressive symptoms and preventing relapse. Feasibility and efficacy of in-person MBCT adapted for pregnant women with histories of depression was demonstrated in a randomized trial (N=86) comparing it to treatment as usual (TAU, Dimidjian, Goodman, MH083866). [40, 41] Results showed high rates of engagement and practice completion, and significantly lower postpartum depressive relapse rates, X2(1) = 6.92, p = .008, and symptom severity, $t(83) = 3.31$, p = .002, d = 0.72, for MBCT compared to TAU.

Figure 1. Perinatal depressive relapse rates for MBCT vs. TAU



Our initial trial of a digital version of MBCT in adults with one or more previous depressive episodes (Segal and Dimidjian, MH0877223) showed that MBCT participants had significant improvements in PHQ-9 symptom severity scores compared to a propensity matched control group (N=100), t(81)=8.22, p=0.005; d=1.79. [34] Our digital version of MBCT adapted for pregnant women (MMBFM) was evaluated in an open trial (N=37) and demonstrated participant engagement and sustained minimal to mild depressive symptom severity over the program. [42]

These findings support further efforts to evaluate effectiveness and implementation of MMBFM in larger representative populations of pregnant women with histories of depression.

C.1.2. Consistent with the experimental therapeutics approach for clinical trials, digital MBCT engages proximal mechanisms underlying intervention effects. Our research on digital MBCT demonstrates that it effectively engages mechanisms underlying depressive symptoms and relapse risk. The trial comparing digital MBCT to propensity matched controls (Segal and Dimidjian, MH0877223) showed that digital MBCT participants had decreases in rumination ($t(39) = 3.03$, $p < .005$, d=0.48) and increases in mindfulness ($t(39) = -2.60$, $p < .02$, d =0.41), with subsequent improvements in PHQ-9 symptom severity scores as noted above. [34] In addition, results from the open trial of MMBFM indicated that a majority of pregnant women "endorsed benefits aligned with relapse prevention program targets, including developing the ability to take action in response to early warning signs of depression, to maintain an increased sense of control over depression and awareness of negative thoughts and emotions, to see thoughts as thoughts instead of facts, and to be mindful", among others. [42] Preliminary findings from our RCT comparing digital delivery of MBCT to UC among 460 adult KPCO members with residual depressive symptoms (Segal, MH102229) also suggest comparable improvements in both proximal markers of symptom elevation and relapse risk and in more distal 12-month outcomes of symptom severity and relapse.

C.1.3. Capacity to recruit pregnant women with mood disorders. Our research team has conducted several pragmatic trials and feasibility studies involving both practice-based and population-based recruitment of pregnant women over the last 10 years, including the evaluation of MBCT for perinatal depression, both in person and online, and training both allied health professionals and peers with lived experience to deliver behavioral activation to depressed pregnant women. [40, 41, 43] These trials have involved KPCO, KPWA, KPGA, and HP, demonstrating our capacity to conduct pragmatic trials efficiently in populations of pregnant women receiving prenatal care in large health systems.

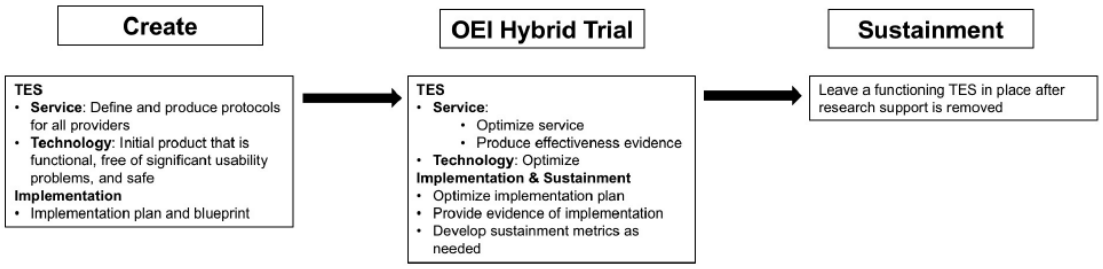
C.1.4. Capacity to conduct large-scale implementation studies. Our research team has extensive experience conducting large-scale multi-site implementation studies of integrated care interventions for depression, and assessing patient, system, and cost outcomes using innovative designs and mixed methods, including Depression Improvement Across Minnesota–Offering a New Direction (DIAMOND, 5R01MH080692-

04),[44] and Care Of Mental, Physical And Substance-use Syndromes (COMPASS, 1C1CMS331048).[45, 46] Our experience with implementation studies provides a strong foundation for conducting the proposed research.

C.2. Method

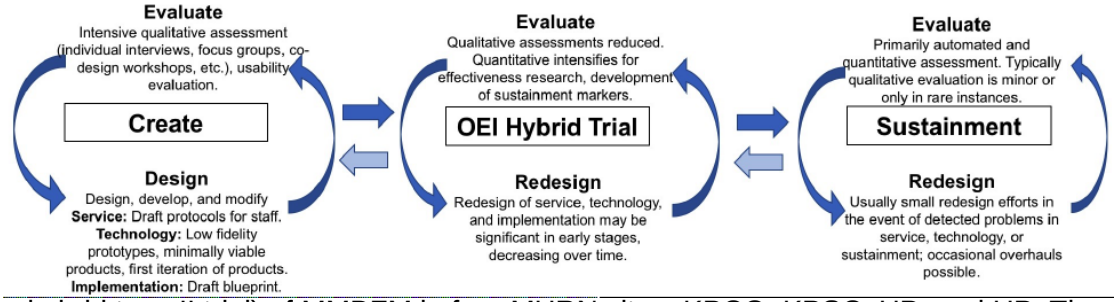
C.2.1 Overview of Study Design. This pragmatic hybrid type II design will be guided by the Accelerated Creation-to-Sustainment (ACTS) model for technology-enabled service (TES) that is sustainable in a real-world treatment setting [37] (figure 2).

Figure 2: Aims for each development target in each phase



The model specifies three phases, with associated sets of activities and related evaluation metrics: 1) create; 2) conduct Optimization, Effectiveness, and Implementation (OEI) hybrid trial; and 3) sustainment. The model is dynamic, involving iterative design, redesign, adaptation, and evaluation functions at each phase (figure 3).

Figure 3: Iterative evaluative and design functions at each phase



We completed phase 1 by creating and conducting preliminary tests of MMBFM with significant provider and patient stakeholder input. We now propose to conduct an OEI hybrid trial (also called a hybrid type II trial) of MMBFM in four MHRN sites: KPCO, KPSC, HP, and HP. The effectiveness component of the hybrid trial will be conducted at the KPCO and KPSC sites using a two-arm randomized design comparing MMBFM to UC on change in the primary outcomes of depression symptom severity and rates of relapse or clinically significant worsening from baseline through 6-months postpartum for women at risk for recurrent depression (see **C.2.2**). The implementation study will be conducted at HP and KPGA using a single cohort design to develop, test, and optimize strategies based on stakeholder input, to increase the reach, adoption, implementation, and maintenance of the MMBFM program (see **C.2.3**). The implementation study will begin after the effectiveness trial to allow for adaptations that may be needed based on experience with the effectiveness trial.

The proposed hybrid effectiveness-implementation design is warranted because evidence of effectiveness of digitally-delivered MBCT for pregnant women is promising but limited, [42] despite strong evidence of efficacy when delivered in-person. [40] In addition, healthcare systems such as those in the MHRN are keenly interested in expanding access to non-pharmacologic interventions for pregnant women (and adults in general) with recurrent depression, but to adopt MMBFM, they must address factors that impede or facilitate implementation and sustainment, and be provided evidence of cost-effectiveness. [47]

C.2.2. Effectiveness trial

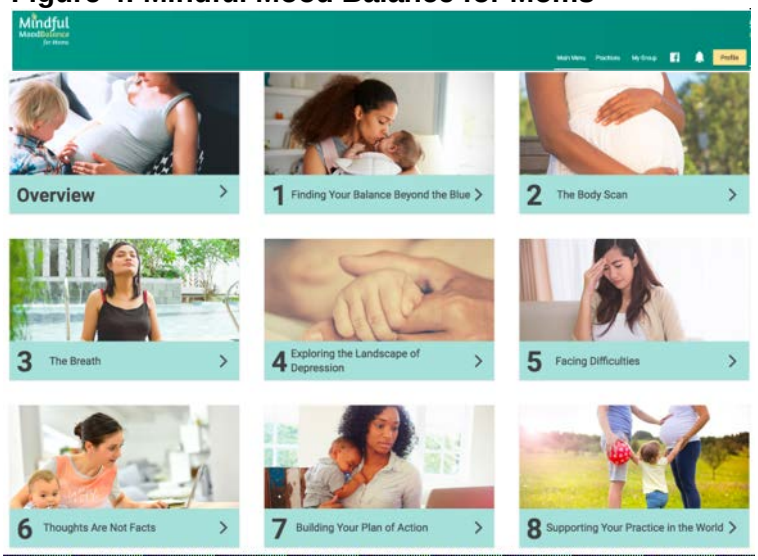
Inclusion/Exclusion Criteria. Consistent with a pragmatic trial, minimal inclusion and exclusion criteria will be used. Participants will be women ≥18 years of age, receiving prenatal care, 12-28 weeks gestation, with at least one prior episode of MDD, and current PHQ-9 score <10. Women with a diagnosis of a psychotic, bipolar, or substance use disorder or at immediate risk of self-harm will be excluded. Currently, the intervention is in English only, therefore patients who are unable to speak and read English will be excluded.

Recruitment, randomization, and consent procedures. The effectiveness trial will involve recruiting and randomizing 460 pregnant women at risk for recurrent depression to receive MMBFM (N=230) or UC (N=230). This sample size is specifically powered to detect group differences for the primary effectiveness outcomes of depression symptom severity and rates of relapse or worsening. Recruitment will be done at each site using electronic medical records to identify potentially eligible women receiving routine prenatal care. Study

participants will be recruited using methods suitable for each site, including bulk email and/or secure message through the EMR patient portal, or by regular mail. The outreach message will contain a link to a recruiting survey containing a description of the study and brief questions to determine initial eligibility, followed by online consent. Women who pass the initial screen and consent will be called by the study staff at KPCO to review the online consent, complete the baseline clinical assessment and be randomized into MMBFM or UC.

MMBFM protocol. The 8-session protocol for MMBFM is based on the theory underlying MBCT as described in **A.3**. The sessions teach mindfulness practice and cognitive behavioral skills to help reduce automatic, depressogenic modes of thoughts, emotions, and sensations. Additions to the standard MBCT curriculum for pregnant women include brief informal mindfulness, social support, and self-compassion practices as well as psychoeducation about mood and anxiety during the transition to parenthood. MMBFM (see Figure 4) is delivered in a mobile first digital format, accessible from desktop or mobile devices, and provided in an individually tailored manner that includes experiential practice, video-based vicarious learning, and didactic information. [48, 49]

Figure 4: Mindful Mood Balance for Moms



Accompanying materials are provided for each session via digital access to forms and audio or video guides identical to those used in standard MBCT, modified for digital format. Participants are asked to logon to the program to complete one session each week and to set a regular routine for sessions and homework practice. Telephonic outreach and coaching supplemented by email check-in and supportive messaging, will be delivered by the KPCO site for the duration of the 8-week intervention, described in an MMBFM coaching manual developed by Dimidjian and colleagues (available upon request). The KPCO site will also moderate site activity, including coaching feedback and online community interactions. Data analytics built into the platform will record the number of sessions completed, frequency of use, and date and duration of logins to MMBFM. self-reported frequency of mindfulness practice will also be recorded within the platform.

Usual Care (UC). Usual care will not be constrained for any study participants, including those randomized to MMBFM. The study will not constrain or influence UC or MMBFM participants' decisions to maintain or discontinue AD or to receive psychotherapy within their respective healthcare systems. Participants in the UC group will receive feedback on their baseline and follow-up assessments (e.g., "Your answers to suggest that you are having significant symptoms of depression. We recommend that you talk with your provider about whether treatment or modification of treatment might help"). In addition, we will implement protocols for each participating healthcare system to ensure that treating providers are notified if participants evidence clinical deterioration (PHQ-9 scores $\geq$15) and/or suicide ideation (endorsement of a score of 2 or 3 on PHQ item 9) on baseline and/or follow-up assessments.

Measures

Data collection will be done using a combination of REDCap (Research Electronic Data Capture, [50] a web-based survey technology) and programming to extract data from electronic medical records and Virtual Data Warehouses (VDWs) at each site. Baseline data will include demographic variables, contact information, current and previous mental health treatment history, and a screener for substance abuse. [51] Depression symptom severity will be assessed with the PHQ-9. [52] The mood module of the *MINI* [53] will be administered at baseline to assess depression diagnoses, prior episodes, and comorbidity.

Intervention Adherence. MMBFM participants will be asked to use a Home Practice Record [54] to monitor mindfulness practices weekly during MMBFM, and monthly through 6-months postpartum.

Clinical and Functional Outcomes. The following self-report measures will be administered at baseline, 16 weeks after randomization, and at 3 and 6 months postpartum: 1) PHQ-9 [52] to assess depression relapse or

clinically significant worsening, defined as a score of >13, and depressive symptom burden; 2) anxiety severity, assessed using the Generalized Anxiety Disorder 7-item Questionnaire (GAD-7) [55]; and 3) functional status, assessed using the SF-12. [56]

Infant outcomes. Preterm birth and gestational age will be measured from perinatal data recorded in the EMR and linked with maternal records.

Maternal outcomes. The Parenting Stress Index-Short Form (PSI-4/SF) [57], and Perceived Maternal Parenting Self-Efficacy Scale (PMP S-E) [58] will be administered at 6 months postpartum.

Intervention Exposure and Satisfaction. Backend website analytics will be used to assess MMBFM exposure. We will use the Client Satisfaction Questionnaire (CSQ-8) [59] to assess perceptions of and satisfaction with MMBFM and UC at 6 months postpartum.

Putative Targets of MMBFM. Putative targets will be measured at baseline, 16 weeks after randomization, and at 3 and 6 months postpartum using the *Five Facet Mindfulness Questionnaire* (FFMQ), [60] a 39-item self-report measure of domains of mindfulness (observing, describing, acting with awareness, accepting without judgment, non-reactivity), and the *Ruminative Response Scale* (RRS), [61] a measure of ruminative responses to negative affect.

Analysis plan

Demographic, clinical, and self-report data for the cohort will be reported with descriptive statistics. Baseline differences between MMBFM and UC will be assessed using Chi-square tests 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 used as covariates in subsequent multivariate analyses. All participants will be included in the analysis (intent-to-treat sample). Significance levels will be evaluated at $p<.05$, and effect sizes reported.

H1a: Reduction depressive symptom burden and relapse or worsening at 6-months postpartum. Hierarchical Linear Models (HLM) will be used to compare change over time between groups on depressive symptom severity using the PHQ-9. Using power estimates for linear mixed models, [62] an effect size of .25, which is much smaller than the .70 effect size observed in our trial of MBCT for pregnant women, [40] two-tailed alpha level of .05, and a within-subjects correlation of 0.5, a sample size of 228 per group will provide 86.5% to detect this difference, allowing for 30% attrition. We will examine time to relapse or clinically significant worsening as measured by PHQ-9 scores >13 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. However, time to attrition is a competing risk that can be related to time to relapse. We will adopt the sub-distribution hazard model (SHM) developed by Fine and Gray to account for the possible nonindependence of the censoring mechanism. [63] In our efficacy study of MBCT, [40] pregnant women who received MBCT evidenced approximately 30% lower rate of relapse/worsening than UC. We will use a more conservative approach estimating 15% lower relapse/worsening rates among MMBFM participants. A sample of 217 participants per study arm is required to detect this difference with 80% power and a two-tailed alpha-level of .05, allowing for an estimated 30% attrition over the 6-month postpartum period.

H1b: (exploratory outcomes): Reduction in stress and anxiety through 6-months postpartum. Hierarchical Linear Models (HLM) will be used to compare change over time between groups on PSS and GAD-7 scores. Though these outcomes are exploratory, we estimate an effect size comparable to that for depression symptom reduction, and therefore expect to have sufficient power to assess these outcomes.

H1c (exploratory outcomes): Higher infant gestational age at delivery, and lower rates of preterm birth. For these exploratory outcomes, we will use HLM to compare differences in mean gestational age between groups and modified Poisson regression to assess differences in preterm birth rates. However, power to detect modest differences in preterm birth will be low (e.g., 10% vs. 15%, will provide 63% power for our sample of 460). [7]

H1d (exploratory outcomes): Better maternal functioning at 6 months postpartum. Analyses of variance will be used to assess group differences PSI-4/SF and PMP S-E scores 6 months postpartum. Effect size estimates for these measures to be comparable to those for H1a and H1b, and we anticipate sufficient power detect group differences in these outcomes.

H2: MMBFM will demonstrate acceptable incremental cost effectiveness relative to the UC group, based on the health care system perspective. We will estimate the cost of delivering MMBFM, the total costs associated with MMBFM relative to UC, costs per participant, and the incremental cost per depression free

days (DFDs) and quality adjusted life year (QALYs) over the 6 months postpartum period. The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in mean cost divided by the difference in the mean clinical outcome (e.g. DFD, QALY). In order to represent uncertainty around the ICER estimate, we will create 1000 bootstrap replications of the data and use these to a create 95% confidence interval. [64] In addition, we will use the bootstrapped data to create a cost-effectiveness acceptability curve to represent the uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would likely consider reasonable. We have used these methods successfully in multiple previous studies. [65-68]

C.2.3. Implementation study

A single cohort design will be used to test the success of implementation strategies at the HP and KPGA sites. Guided by the OEI phase of the ACT model, implementation site investigators will identify key stakeholders from obstetrics, behavioral health, and health system administration, as well as women with lived experience of perinatal depression, to collaboratively develop site-specific implementation and sustainment plans for the MMBFM program. Key stakeholder interviews will be conducted to provide qualitative data on local context to inform these plans. Strategies to facilitate implementation and sustainment of MMBFM may include broadening inclusion criteria (e.g., recruiting all antenatal women with PHQ-9 scores <10 vs. those with histories of depression and residual symptoms; including antenatal women with moderate to high anxiety, i.e., GAD-7 scores ≥10, etc.), testing different recruitment methods (population-based vs. referral-based), and modifying the MMBFM coaching protocol (e.g., using digital vs. telephonic coaching), among others.

Recruitment and enrollment procedures. We plan to recruit and enroll approximately 1,200 women to participate in the MMBFM program, based on a proposed reach metric of 25% of an estimated 4,600 eligible pregnant women receiving prenatal care within one year at the two implementation sites. Recruitment procedures for the implementation study will be similar to the effectiveness trial but modified according to stakeholder preferences as described above. In addition, enrollment and assessment procedures will be more limited than for the effectiveness trial in order to more closely resemble conditions for real-world implementation in healthcare systems. For example, baseline assessment of past depressive episodes will be done via a self-report question ("Have you ever had a period when you were feeling depressed or down most of the day nearly every day for two weeks or more or you were a lot less interested in most things or unable to enjoy the things you used to enjoy?"). [11] In addition, we will not randomize women to UC or collect data on perinatal or postpartum outcomes. Instead, outcome assessment using the PHQ-9 and GAD-7 (embedded in the MMBFM program) will done following completion of MMBFM.

Measures and analysis

Hypothesis 3: MMBFM will show meaningful reach, adoption, implementation, and maintenance. The RE-AIM model will be used to evaluate specific implementation outcomes for MMBFM. Although there are no common metrics for implementation outcomes related to digital mental health interventions, we propose metrics based on our experience with previous implementation studies, and that are meaningful from a population health perspective. Descriptive and qualitative analyses (based on stakeholder interviews) will be done to assess representativeness of MMBFM participants and referring providers, reasons for the outcomes observed (e.g. patients' reasons for not participating in MMBFM or OB providers' reasons for not referring patients to MMBFM), and any adaptations made to increase values for these implementation outcomes:

Reach: 25% of eligible women contacted or referred will participate in MMBFM.

Effectiveness: the primary effectiveness outcome will be assessment of differences between MMBFM vs. UC groups in symptoms of depression and rates of relapse or worsening, as described in Aim 1. Secondary outcomes will include group differences in anxiety symptoms, infant outcomes, and maternal function.

Adoption: 30% of OB providers within and across implementation sites where MMBFM is offered will refer eligible patients to the program after the initial recruitment phase for the trial is completed. Survey questions attached to the MMBFM program will ask participants about referring OB providers and clinics.

Implementation: 40% of patients who initiate MMBFM will complete at least 4 sessions of the program (minimal dose shown to be effective), as assessed by website usage statistics.

Maintenance: Implementation sites will decide to offer MMBFM as a preventive treatment option for women at risk for perinatal depression.