Mindful Moms in Recovery: Yoga-based mindfulness relapse prevention for women with opioid use disorder

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TABLE OF CONTENTS

Page

Mindful Moms in Recovery: Yoga-based mindfulness relapse prevention for 1

women with opioid use disorder 1

Tool Revision History 2

TABLE OF CONTENTS 3

STUDY TEAM ROSTER 6

PARTICIPATING STUDY SITES 7

1.0 STUDY OBJECTIVES 8

1.1 Aim 1: Primary Objective. 8

1.2 Aim 2: Primary Objective. 8

1.3 Aim 3: Primary Objective. 8

2. BACKGROUND AND RATIONALE 9

2.1 Background on Condition, Disease, or Other Primary Study Focus 9

2.2 Study Rationale 10

3. STUDY DESIGN 12

4. SELECTION AND ENROLLMENT OF PARTICIPANTS 14

4.1 Inclusion Criteria 14

4.2 Exclusion Criteria 14

4.3 Study Enrollment Procedures 14

5.1 Interventions, Administration, and Duration 14

5.2 Handling of Study Interventions 15

5.3 Concomitant Interventions 16

5.3.1 Allowed Interventions 16

5.3.2 Required Interventions 16

5.3.3 Prohibited Interventions 16

5.4 Adherence Assessment 16

6. STUDY PROCEDURES 16

6.1 Schedule of Evaluations 17

6.2 Description of Evaluations 18

6.2.1 Screening Evaluation 20

Consenting Procedure 20

6.2.2 Enrollment, Baseline, and/or Randomization 21
6.2.3 Blinding 22
6.2.4 Contamination 23
6.2.5 Follow-up Visit 23
6.2.6 Completion/Final Evaluation 23

7. SAFETY ASSESSMENTS 23

7.1 Specification of Safety Parameters 23

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters 25

7.3 Adverse Events and Serious Adverse Events 26

7.4 Reporting Procedures 26

7.5 Follow-up for Adverse Events 26

7.6 Safety Monitoring 27

8. INTERVENTION DISCONTINUATION 27

9. STATISTICAL CONSIDERATIONS 27

9.1 General Design Issues 27

9.2 Sample Size and Randomization 28
Treatment Assignment Procedures 29

9.3 Definition of Populations 29

9.4 Interim Analyses and Stopping Rules 29

9.5 Outcomes 29
9.5.1 Primary Outcome 29
9.5.2 Secondary Outcomes 29

9.6 Data Analyses 30

10. DATA COLLECTION AND QUALITY ASSURANCE 32

10.1 Data Collection Forms 32

10.2 Data Management 32

10.3 Quality Assurance 32
10.3.1 Training 32
10.3.2 Quality Control Committee 32
10.3.3 Metrics 32
10.3.4 Protocol Deviations 33
10.3.5 Monitoring 33

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY 33

11.1 Institutional Review Board (IRB) Review 33

11.2 Informed Consent Forms 33

11.3 Participant Confidentiality 33
11.4 Study Discontinuation 34

12. COMMITTEES 34

13. PUBLICATION OF RESEARCH FINDINGS 34

14. REFERENCES 34

15. SUPPLEMENTS/APPENDICES 35

I. Procedures Schedule

II. Informed Consent Form Template

III. Other (add as many appendices as necessary)

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1.0 STUDY OBJECTIVES

In this R33 phase of the project, we will conduct a randomized controlled trial to evaluate the efficacy and implementation of the *Mindful Moms* intervention with a sample of pregnant women with identified opioid use disorder receiving medication for opioid use disorder at partner maternity care practices. We will evaluate the impact of *Mindful Moms* as an adjunct to treatment as usual on retention in medication for opioid use disorder (MOUD) treatment, substance use, and relapse-related risks. This study has three Specific Aims:

Aim 1: Evaluate MMORE in a randomized controlled study with pregnant women as an adjunct to MOUD treatment as usual care for impact on treatment retention, opioid abstinence, and relapse risks.

Aim 2: Examine mechanisms of effect of MMORE on outcomes.

Aim 3: Evaluate barriers and facilitators to sustainable implementation of MMORE as an adjunct to MOUD for pregnant and parenting women.

1.1 Aim 1: Primary Objective.

To assess the efficacy of MMORE on maternal treatment and well-being outcomes.

Primary endpoints:

1) *MOUD treatment retention*
2) *Opioid abstinence*

Secondary endpoints:

1) *Other illicit substance use*
2) *Psychological wellbeing (depression, anxiety, posttraumatic stress)*
3) *Mindfulness*
4) *Quality of life*
5) *Pain perception*

1.2 Aim 2: Primary Objective.

To identify factors associated with change in endpoints to inform targets for intervention.

Primary endpoints:

1) *MOUD treatment retention*
2) *Opioid abstinence*

1.3 Aim 3: Primary Objective.

To identify barriers and facilitators to implementation of the intervention to guide development of strategies to overcome barriers in future work.

Primary endpoints: Endpoints for this non-powered exploratory aim are key implementation outcomes, including: 1) Intervention Acceptability, 2) Feasibility, 3) Fidelity, 4) Reach, and 5) potential for Sustainability within practice infrastructure.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Prevalence of OUD among pregnant and parenting women in NH is high and costs of untreated OUD are high. Perinatal OUD is described as a national public health epidemic, and NH is no exception.8 Roughly 40% of recent opioid overdose deaths in the state were women, and 21% of pregnancy-associated deaths between 2013-2015 were attributed to overdose. An estimated 8-10% of deliveries in NH are affected by perinatal OUD. Rising prevalence rates indicate that NH can anticipate as many as 1,000 infants born with prenatal opioid exposure each year. Perinatal OUD is associated with increased morbidity and mortality for both mother and infant due to infectious disease, higher rates of prematurity and pregnancy complications, low birth weight, neonatal abstinence syndrome (NAS), and social stressors such as homelessness, poor nutrition, and criminal justice involvement. In 2012, nearly 22,000 neonates in the U.S. were born with NAS, translating to one neonate born every 30 minutes and resulting in $1.5 billion in hospital charges nationwide. Prenatal substance exposure and untreated postpartum maternal substance use are associated with developmental disorders and risk of adverse childhood experiences for children, which are strong predictors of later adolescent and adult substance use disorders and related health consequences.

The current standard of care for treatment of OUD during pregnancy is medication for opioid use disorder (MOUD) with methadone or buprenorphine. Evidence indicates buprenorphine improves neonatal outcomes compared with methadone in terms of lower NAS risk, shorter NAS treatment duration and mean length of hospital stay, higher mean gestational age, and greater weight, length, and head circumference at birth. Medication is most effective in combination with counseling, care management, and psychosocial support to address the complex array of individual and social factors that can adversely impact treatment compliance and the health and wellbeing of women and their children. Expansion of MOUD in obstetric settings for pregnant and parenting women with OUD is a targeted priority of the NH State Targeted Response (STR) to the opioid crisis.

Early postpartum period presents increased risk for MOUD discontinuation. Even when treatment is initiated, there is a high rate of discontinuation, particularly during the early postpartum period. In a recent systematic review, prenatal discontinuation rates ranged from 0-33%, and postnatal rates from 26-64%. In a well-established integrated perinatal obstetric-MOUD program in NH, MOUD discontinuation was 40% at 3 months postpartum, with the greatest drop-off evident between 6 weeks and 3 months postpartum. Much of the extant literature focuses on methadone discontinuation and there is a need for research on treatment retention among women receiving buprenorphine, particularly during the early postpartum period. The proposed project aims to address this research gap.

Pain management is complicated for pregnant and parenting women with OUD. Pain management, already a common concern for intrapartum and postpartum care, is complicated in the context of opioid dependence. In addition to natural pregnancy-related pain (e.g., leg and lower back pain, musculoskeletal pain), chronic pain (e.g., endometriosis, traumatic injury) is often part of the clinical portrait of women with substance use disorders. The limited literature regarding perinatal pain management for women with OUD indicates that pregnant women on MOUD can experience cross-tolerance for other pain medications, requiring more medication to manage pain. Increased sensitivity to pain (hyperalgesia) is also a hallmark of long-term opioid use, also necessitating use of more intensive pain management strategies. Mental health conditions can exacerbate patients' experiences of pain, and sleep quality, a critical component of wellbeing, is negatively affected by pregnancy and opioid dependence. Poor sleep quality is associated with increased sensitivity to pain and is a risk factor for relapse. Several studies suggest that pain management for women with OUD deteriorates postpartum, such that women on MOUD experienced increased pain postpartum compared with opioid-naïve women. Under-treatment of pain can significantly increase risk of relapse. Accessible non- pharmacological approaches to pain management may offer an important adjunct to recovery support for pregnant and parenting women with OUD.

2.2 Study Rationale

Yoga and mindfulness-based intervention approaches are promising candidates for supporting recovery for women with OUD. There is growing evidence for the positive impact of these contemplative practices for pregnancy, trauma, mental health, pain, and substance use disorders.

Yoga and pregnancy. Yoga interventions may differ in specific orientation, but most are organized around three core components: 1) gentle movement, poses, and stretches to support balance, flexibility and body awareness, 2) focus on breathing, and 3) using breath and sensations within the body to anchor attention to the present moment. Recent reviews of yoga interventions with pregnant women indicate consistent improvements in psychological domains during pregnancy and labor (e.g., depression, anxiety, perceived stress, quality of life and self-efficacy), in physical and pain measures during pregnancy and labor (e.g., discomfort and pain), and in birth variables (e.g., birth weight and number of preterm births). In one randomized controlled study, a single session of yoga reduced state anxiety and cortisol level in depressed pregnant women, and this reduction was maintained throughout the intervention. In another study, women who received a daily yoga and relaxation protocol experienced significantly greater reductions in perceived stress and improvements in reactivity to stress (i.e., increased heart rate variability) relative to those who did not receive the intervention. The positive effects of yoga on depression can extend into the postpartum period.

Yoga and trauma. Emerging evidence supports yoga as an adjunct to care of trauma. Trauma-informed yoga incorporates elements to be sensitive to presenting features of trauma experiences and posttraumatic stress disorder, such as hypervigilance and feelings of not being in control. This approach fosters client choice in all aspects of the practice and sets clear expectations to help clients anticipate what is going to happen from one moment to the next. A randomized controlled trial of a trauma-informed yoga intervention produced greater improvement on PTSD and depression symptom severity relative to a health education class among women with treatment-resistant PTSD. Frequency of yoga practice beyond the study period was associated with greater and prolonged improvements. In another study, participants with PTSD who

received a Kundalini yoga intervention experienced greater improvement in measures of sleep, positive affect, perceived stress, anxiety and resilience relative to an assessment control.

Mindfulness and pregnancy. For purposes of this proposal, we refer to mindfulness-based interventions derived from the evidence-supported Mindfulness-Based Stress Reduction Model (MBSR). This 8-session meditation protocol focuses on promoting awareness, acceptance, and non-judgment of thoughts, feelings, and experiences. The MBSR program follows a structured format curriculum taught in a group format over 8 weeks, with practices to help participants develop moment-to-moment awareness and acceptance. Participants develop skills to become nonjudgmentally aware of thoughts, feelings, and sensations, and increase their capacity to replace automatic and judgmental reactions with more conscious responses. Mindfulness practices include sitting and walking meditation, body scan exercises, body awareness movement, and guided meditations. A recent systematic review of research on mindfulness-based interventions in pregnancy described consistent effects in favor of mindfulness for improvement of depression, anxiety, stress, and mindfulness awareness among pregnant and postpartum women. Pilot studies of a mindfulness-based yoga protocol combining yoga with MBSR for pregnant women produced reductions in physical pain and stress, and improvements in sleep quality.

Mindfulness and substance use. Mindfulness-based interventions for addictive behaviors, such as Mindfulness-Based Relapse Prevention (MBRP), include content targeting awareness and reactions to craving and adverse cognitive, affective, or physical states that trigger use and focus of attention on positive experiences and rewards. Meta-analyses of mindfulness intervention studies indicate small-to-large effects of mindfulness treatments for reducing frequency and severity of substance use, intensity of drug craving, severity of stress, and negative consequences of use. Few mindfulness intervention studies have focused specifically on women with substance use conditions. In one study comparing MBRP with standard relapse prevention with women offenders at a residential addiction treatment center, women in MBRP reported significantly fewer drug use days and fewer legal and medical problems at follow-up. A pilot study of mindful awareness body touch-therapy (MABT) as an adjunct to substance use treatment for women yielded moderate to large effects, including significantly fewer substance use days, and improvement in eating disorder symptoms, depression, anxiety, dissociation, and perceived stress compared to treatment as usual. There are no published yoga or mindfulness-based intervention studies with pregnant women with OUD. We intend to address that significant gap in the proposed project.

Toward an integrated yoga-based mindfulness approach for pregnant women with OUD. The available evidence indicates that yoga and mindfulness-based interventions are well indicated for pregnant women with OUD at a vulnerable time of tremendous change in their bodies. These complementary contemplative approaches share a focus on promoting present awareness of physical, emotional, and cognitive sensations and experiences and fostering skills to manage challenging experiences. Yoga practice specifically emphasizes building interoceptive awareness (i.e., awareness of body sensations) through poses and breathing. Building interoceptive awareness may be particularly important for pregnant women with OUD, since many of these women have experienced trauma, and body dissociation is a common clinical experience of trauma. Interoceptive awareness is important for cognitive processes underlying emotion regulation, and interventions aimed at facilitating such awareness may facilitate regulation and improve substance use treatment. The demonstrated benefits of yoga for pregnant women

indicate that the approach for this population of women can not only build balance, strength and flexibility, reduce psychological distress, and promote overall health and wellbeing, but may also foster important interoceptive awareness to help support ongoing recovery. Anecdotal reports from NH women in recovery indicate diminished self-care as a strong precursor to relapse. An integrative approach that synergistically harnesses the beneficial elements of both approaches could align well with the needs of pregnant and parenting women with OUD.

The project addresses a notable gap in research of yoga-mindfulness intervention approaches with pregnant women with OUD. To the best of our knowledge this will be the first yoga-based mindfulness relapse intervention developed specifically for this population. Our partnership with the NH Bureau of Drug and Alcohol Services (the NH STR Lead) will ensure that the project maximizes efficiencies with the state STR initiative. The planned activities respond to the priorities of RFA-AT-18-002 in a number of important ways, including focus on implementation of an innovative behavioral intervention as an adjunct to MOUD to promote treatment retention and opioid abstinence, and reduce relapse risks. If MMORE is feasible to implement, acceptable to women, and demonstrates positive impact on outcomes, it will offer a cost efficient and scalable adjunct to MOUD to promote ongoing recovery and wellbeing of pregnant and parenting women with OUD receiving care in women's health settings.

3. STUDY DESIGN

Activities to meet Aim 1. We will evaluate MMORE in a two-group randomized controlled design comparing treatment as usual (TAU) in partner maternity care practices with TAU + MMORE.

Participants will be 150 English-speaking consenting pregnant women aged 18 years and over who have a confirmed singleton pregnancy and are receiving perinatal services and medication for opioid use disorder at partner maternity care practices. We will aim to recruit women in their 2nd/early 3rd trimester of pregnancy.

After completion of the baseline assessment, consented participants will be randomly assigned to participate in the 8-session virtual yoga-mindfulness group intervention or to receive TAU only.

All intervention participants will be provided with a unique password-protected access link to the digital support materials, as well as detailed instructions for how to access the materials. A unique study code will allow us to monitor individual participant use of the support modules for analytic purposes.

All consented participants will complete assessments at baseline, post-intervention (8 weeks for TAU participants) and 3 months postpartum. Participants will complete assessments via a secured, de-identified and password-protected link accessed either on a study-provided laptop computer at a scheduled practice visit or via a protected email link to the user for completion at home or on another secure device with Internet access. Assessments will take approximately 20 minutes to complete. Based on formative data from phase 1 of this project, and other work the research team has conducted with the target population, we anticipate most women will have some access to the Internet either via a mobile phone, tablet, or home computer. If a participant cannot complete an assessment online, a paper version will be provided. The study staff will track ways that participants complete assessments. Participants will receive local gift cards for completion of each assessment.

Activities to meet Aim 2. All study participants (TAU and TAU+MMORE) will complete brief mobile assessments at the end of each week of their assigned cohort period. Assessments will be completed using either a mobile device or computer. Participants will receive a prompt (near end of the week) to complete the assessment. The encrypted, password-protected weekly brief assessment will include items to assess the following:

- Desire for opioids: A single item, "Did you experience craving for opioids at any point this week?", anchored on a 10-point scale (0=Not at all; 10=Extremely).
- Mood: Affect will be assessed by representative items from the Positive-Negative Affect Scale (PANAS), adapted to a weekly time orientation.
- Stress will be assessed by a single item "How would you rate your overall level of stress this week?", anchored on a 7-point scale (No Stress – Worst possible stress)
- Mindfulness. Three mindfulness constructs will be assessed with items from the Awareness (2 items) and Non-Reactivity (2 items) subscales of the Five Factor Mindfulness Questionnaire, and from the Acceptance and Action Questionnaire (2 items).

Activities to meet Aim 3 (Exploratory). A focused implementation evaluation will be conducted with the goal of informing actionable strategies to promote sustainability of MMORE after the NH STR funding has ended. We will use mixed methods to evaluate implementation of MMORE and will draw from implementation science frameworks to guide evaluation. We will use implementation metrics as well as surveys and interviews with participants and obstetric practice stakeholders to evaluate implementation.

At the end of each virtual 8-session intervention period, MMORE participants will complete a Satisfaction Survey regarding their experience (1 to 7 response scale), including: how much liked the intervention, how much the intervention improved awareness of stress and craving triggers, perceived level of confidence to use strategies for awareness, use of acceptance and non-judgment when experienced stress, negative affect and cravings, extent to which intervention helped participant think about their coping strategies and sources of support related to parenting, and likelihood of recommending the intervention to a friend.

We will use the Consolidated Framework for Implementation Research (CFIR) as a conceptual model to guide assessment of barriers and facilitators to implementation and sustainability of MMORE. Interview guides will be constructed with items from the CFIR repository (www.cfir.org) used in other studies. Interviews will tap perspectives related to the intervention itself, attitudes of women with OUD and obstetric and MOUD provider stakeholders about the yoga-mindfulness approaches, and federal and NH state policies (i.e., reimbursement, NH STR initiative) that could support or impede continued offering of the intervention.

Research staff trained in qualitative methods will conduct brief interviews with a subset of study participants (n=30) after the intervention period to obtain perspectives on experiences with MMORE and specific ways the intervention was useful for supporting recovery goals. Interviews will be audio recorded for later transcription and coding.

Trained research staff will also conduct brief interviews with maternity care and treatment provider stakeholders (n=20) from partner practices to obtain perspectives on facilitators and barriers to adoption of MMORE as an adjunct to MOUD for their patients. The interviews will be audio-recorded, transcribed, and coded.

Practice stakeholders will also complete the Organization Readiness for Implementing Change (ORIC), a 12-item measure of change commitment and change efficacy with demonstrated strong psychometrics and the Program Sustainability Assessment Tool, a 40-item measure to assess domains of practice capacity for sustaining an innovation, including political support, funding stability, partnerships, evaluation, adaptation, communications and strategic planning.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Eligible participants will be women, 18 years of age or older, English-speaking, carrying a singleton pregnancy, and receiving medication for OUD treatment as part of prenatal care at a partner maternity care practice.

4.2 Exclusion Criteria

Exclusion criteria include:

- Cognitive or psychiatric impairments that prohibit being able to provide informed consent.
- Any physical conditions that prohibit activity such as gentle yoga.
- Based on our experience with this population, we anticipate that most women will have access to a computer or mobile phone to access the digital support features of the intervention. For those without such access, we will provide a device and data plan to support participation.

4.3 Study Enrollment Procedures

Recruitment will occur by way of flyers placed in well-trafficked areas, information sheets provided to potential participants, and clinician referral at partner practices. Women who express interest will be contacted by a study staff member to arrange for a virtual meeting (by phone or video) to obtain consent and complete the baseline assessment, if eligible. Consented participants will then be randomized, by the lead project coordinator using a standard randomization process, in equal proportions to receive the intervention (MMORE) or treatment as usual condition. The lead project coordinator will meet virtually with participants to explain the study procedures and provide instructions to the digital support features (Intervention Only).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Mindful Moms: Yoga Mindfulness Intervention. The significant restrictions to in-person delivery of services at practice partner settings and continued institutional barriers to in-person research at partner settings due to the ongoing Covid pandemic have necessitated the need for alternative safe intervention delivery strategies for the Mindful Moms intervention. After consultation with our partner practice stakeholders and women with lived experience from our study advisory committee, we are modifying the intervention delivery mode to include virtual delivery of the intervention. We will deliver the group intervention virtually through a secured

Dartmouth-based video conferencing software (Zoom). The virtual intervention protocol will be 8 sessions, approximately 60-minutes in duration, conducted over the course of 10 weeks. Lead Instructor Black, professionally trained and certified in prenatal and trauma-informed yoga, will implement the group protocol sessions at the designated location. Sessions will be attended by at least one study team member. Sessions will be video or audio recorded (participants de-identified) to allow for assessment of fidelity in delivery of protocol.

All intervention participants will be provided with a tablet and mobile hotspot if needed in order to be able to access the virtual intervention sessions. All intervention participants will complete a training with research study staff about how to use the videoconferencing software. All intervention participants will be provided with a unique password-protected access link to the online support materials, as well as detailed instructions for how to access the materials. A unique study code will allow us to monitor individual participant use of the support modules for analytic purposes.

We have developed a safety protocol (overseen by Drs. Goodman and Frew) to ensure strict attention to safety for women participating in the yoga intervention. As with other gentle yoga protocols, the safety protocol will include specific directions by the Intervention Instructor that participants do not have to partake in any of the poses or activities that feel uncomfortable, and adjustments will be made as needed to minimize discomfort for those participants that would like such adjustments. Lead Instructor Black has over six years of experience leading trauma-sensitive yoga protocols with pregnant incarcerated women, a vulnerable population similar to that for the proposed project.

The Lead Instructor will complete the Session Event Checklist after each intervention session to denote any adverse events (non-serious and serious) that take place during the intervention sessions. Participants will complete the Intervention Experience Form at the end of each session to document experience of any adverse events including physical experiences (e.g., shortness of breath, pain, increased or decreased infant movement, or other discomfort experiences during the session) and psychological experiences (e.g., emotional flooding, uncontrollable crying). At the end of each intervention week, all participants will also complete a Weekly Monitoring Form that will include items related to any additional experience of adverse physical or psychological events. The project coordinator will administer the Weekly Monitoring Form by telephone or e-mail.

In the event that a study participant lapses or relapses during the study period, cases will be handled on an individual basis, which may be largely determined by the procedures of the partner maternity care practice in terms of preference for ongoing care. A lapse/relapse will not necessarily lead to participant discontinuation in the study.

Treatment as Usual. Treatment as usual is operationalized as the integrated medication assisted treatment being provided at the partner practice as part of the New Hampshire State Targeted Response 21st Century Cures initiative. Such treatment includes medication for opioid use disorder, individual and/or group counseling, and case management.

5.2 Handling of Study Interventions

All study yoga instructors will be trained on the use intervention protocol and will deliver the

protocol according to the procedures outlined in the Mindful Moms Intervention Manual. The manual outlines the theme and activities of a given session, as well as the content of the companion digital components aligned with the session.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All consented participants will also be receiving treatment as usual at partner practices, which includes medication for opioid use disorder as well as individual and/or group counseling and case management.

5.3.2 Required Interventions

All participants will be receiving medication for opioid use disorder as part of integrated prenatal care at partner maternity care practices.

5.3.3 Prohibited Interventions

There are no prohibited interventions for this study. To account for contamination that may impact outcomes, the study team will document any other research or quality improvement initiatives that may be taking place at the partner practice that could impact study outcomes.

5.4 Adherence Assessment

Tracking intervention session attendance. The study lead project coordinator and the yoga instructor will track participant attendance at intervention sessions. The lead project coordinator will sign in each participant to the virtual intervention sessions using their unique study identification number.

Tracking use of digital features. Technology usage tracking features are incorporated in the digital website to monitor frequency of usage and features most accessed.

Tracking of TAU adherence. Participant adherence to TAU adherence (medication and group/individual counseling) will be evaluated at the end of the study intervention period through self-report and clinical record review.

Monitoring fidelity. Intervention sessions will be video recorded (with participants de-identified) to allow for assessment of fidelity and inter-teacher consistency in delivery of the intervention protocol. Fidelity will be assessed monthly by a team of coders led by the lead project coordinator, all having been trained to identify key content- and style-related components of the yoga-mindfulness intervention, using an appropriately adapted version of the Mindfulness-Based Relapse Prevention Adherence and Competence Scale (MBRP-AC), developed in consultation with MBRP scientist and project consultant Witkiewitz. Adherence to intervention protocol will also be documented by progress notes taken by study staff who attended the session.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	BL	Intervention	Post	3M PP	Final Evaluation
Eligibility: Consent/Enrollment	X				
Demographics	X				
Current physical conditions that could be considered AE	x				
Opioid Abstinence	X		X	X	
MOUD Treatment Retention	X		X	X	
Depression	X		X	X	
Anxiety	X		X	X	
Stress	X		X	X	
Mindfulness	X		X	X	
Pain Perception	X		X	X	
Quality of life	X		X	X	
Substance use (past 3 months, past 30 days)	X		X	X	
Weekly Assessments (craving, mood, stress, mindfulness)		X			
Adverse Events		X	X	X	
Experiences of Care (qualitative)				X	
Fidelity, Acceptability, Reach, Feasibility, Sustainability (Practice Level)					X
Organization Readiness for Implementing Change (Practice Level)	X				X
Program Sustainability (Practice Level)					X

6.2 Description of Evaluations

Outcomes. Participant outcomes will be assessed by way of clinical record review of consented participants and participant self-report. Implementation outcomes will be assessed through intervention usage data, and quantitative and qualitative methods.

Clinical Record Data Collection Procedures: The trained lead project coordinator will conduct chart reviews using approved data collection procedures the research team has used in other studies with this target population. Chart reviews will be conducted at intervals corresponding to 3 months postpartum for participants.

As used in other approved studies conducted by the study team, the research team will work with each practice partner to identify the best strategy for conducting chart review for consented study participants. The practice will provide the identified record list and the lead project coordinator will create a master-code that includes only the respective record numbers and unique study IDs. The master-code will be stored in separate, secured location at the respective partner practice and will only be referred to by the research team for the purposes data quality to ensure completeness of the research database.

The lead project coordinator will collect the chart data using a REDCap Clinical Data Collection template that includes only the corresponding unique study ID. All chart review data collection will occur at the partner practice location and the de-identified research data will be stored on the secured, HIPAA-compliant Dartmouth College REDCap server.

The master-code will be the only linkage between the unique study identifiers contained in the database and the patient record identifier. Upon completion of all data collection and analyses, the master-code will be destroyed so there will be no link to identifiable records in the study. We will not collect any individual identifiers as part of the research database. The single source of PHI (MRN) will be associated only with the unique study ID in the master-code. The PHI will be accessible only to the principal investigator and authorized study staff. The PHI will not be disclosed to any other person or entity.

Clinical Record Data Indicators. The following assessment metrics will be collected from clinical records of consented participants:

Primary End Points:

MOUD Treatment Retention. Treatment retention will be operationalized as a composite of medication adherence (number of weeks buprenorphine or methadone present in the urine toxicology report) and treatment adherence (number of weeks attended required counseling as part of comprehensive treatment as usual, as indicated in clinical notes) - throughout the prenatal period to 3 months postpartum.

Opioid use abstinence. Weekly point of care urine toxicology screening is conducted as part of standard care with all MOUD patients at partner practices to assess for THC, cocaine, benzodiazepines, methamphetamine, opioids, methadone and buprenorphine. Opioid abstinence will be measured as number of weeks consistently abstinent from opioids over the perinatal period to 3 months postpartum.

Secondary End Points:

Other substance use. Other substance use will be measured as number of weeks the participant used marijuana and/or other drugs as indicated in urine toxicology reports. Tobacco and alcohol use will be measured by way of documentation in clinical notes from visits.

Participant Self-Report Procedures: Participants will complete secured online survey assessments at baseline, post-intervention, and 3-months postpartum. The project coordinator will ensure that participants receive the assessment surveys at the specified times in the manner preferred by the participant. If participants wish to receive the survey via email, the survey will be sent as a unique study-identified password-protected link. The project coordinator will monitor and track survey assessment completion and ensure that participants receive gift card incentives for survey completion in a timely manner. For participants who do not wish to complete the survey online, the project coordinator will arrange for either a phone interview with the participant to complete the survey or will mail the participant the survey along with a self-addressed and stamped envelope for the participant to return the survey. The assessment survey will include the following:

Primary End Points:

Treatment Retention. Self-reported adherence to medication for opioid use disorder will be assessed by an adaptation of items from the well-established Adherence to Medication questionnaire originally developed for assessing adherence to antiviral medications among persons with HIV/AIDS. (i.e., when was the last time you skipped buprenorphine medication? [past 2 days, within the past 2 weeks, 2-4 weeks ago, 1-3 months ago, never skipped past 3 months]. Participants will also report how often they attended group/individual counseling in the past 3 months [every week, every other week, once a month, less than once a month].

Opioid abstinence. The reliability of self-report of substance use for pregnant and parenting women is especially complicated due to well-founded fears of child protective service involvement and potential loss of children. That said, when research studies are well-conducted and assurances for protection of participant privacy are clear and conveyed with messaging informed by community partners with lived experience, women do reliably self-report their use behaviors.

Opioid use will be assessed with relevant items from the Alcohol, Smoking and Substance Involvement Screening Test, aligned with relevant timeframes (baseline: past 6 months, post-intervention and 3 month postpartum: past 3 months). Opioid use disorder severity will be assessed with items corresponding to DSM-V diagnostic criteria.

Secondary End Points:

***Other substance use*:**
Self-reported frequency and quantity of opioid and other substance use (including alcohol, marijuana, and tobacco) will be assessed with the Alcohol, Smoking and Substance Involvement Screening Test, aligned with relevant timeframes (baseline: past 6 months, post-intervention, 3 month postpartum: since last survey).

***Mental Health*:**

Depression will be assessed using the Edinburgh Prenatal and Postnatal Depression Scales, both of which have been used extensively with the target population.

Anxiety will be assessed with the Generalized Anxiety Disorder Scale (GAD-7)[2], a psychometrically sound instrument routinely used in general health care settings.

Stress will be assessed with the Perceived Stress Scale,[3] a psychometrically sound instrument that has been used in other studies of contemplative interventions with pregnant women[4-7].

Posttraumatic stress will be assessed with the abbreviated PTSD Checklist (PCL-5), a screening instrument developed for primary care and other general medical settings, and used in studies with the target population.[8]

Mindfulness. Mindfulness will be assessed with the Mindful Attention Awareness Scale. This instrument has been used with demonstrated good psychometrics in mindfulness intervention studies with pregnant women and substance-using populations[9-12].

Quality of Life. Quality of life will be assessed with the World Health Organization QoL BRF, a widely used instrument with demonstrated validity and reliability with pregnant and early postpartum women.

Pain Perception. Pain Perception will be assessed by a widely used visual analog scale (VAS) used in other studies with pregnant women. Participants report point areas and levels of pain on a scale from 0 (no pain) to 10 (worst possible pain) and anchored with descriptive faces.

Implementation Outcomes. Endpoints for this non-powered exploratory aim include: 1) Intervention Acceptability, 2) Feasibility, 3) Fidelity, 4) Reach, and 5) potential Sustainability within practice infrastructure.

6.2.1 Screening Evaluation

Consenting Procedure

Interested participants will contact one of the project coordinatorss via email or phone to review the study procedures.

The project coordinator will review all aspects of the ICF with the candidate, checking for comprehension throughout, and will answer the candidate's questions. Additionally, the project coordinator will offer the candidate the opportunity to personally read the ICF over in more detail and will provide the candidate sufficient time to review and ultimately decide if she is willing to participate.

Assessing Comprehension

After allowing the candidate to review the ICF, and answering any preliminary questions, the project coordinator may ask the candidate the following questions to assess comprehension:

- Please describe in your own words the purpose of this study.
- Just so that I'm sure you understand, please explain to me what you think we're asking you to do.
- What is the possible benefit to you of participating in this study? What are the possible risks?
- What more would you like to know?

If the candidate answers all questions correctly, the project coordinator will answer any additional questions and the participant will indicate consent by marking the check box on the consent form. A waiver of signed consent was requested and approved by the Dartmouth IRB. The project coordinator will sign the consent form to indicate witness of consent and will provide the participant with a duplicate of the consent form.

If the candidate answers any questions incorrectly, the project coordinator will review the correct responses with candidate until comprehension is ensured and then proceed with obtaining consent.

If, after assistance and review of correct responses, the candidate is unable to demonstrate a basic understanding of the study, the candidate will be deemed ineligible to participate in the study. The project coordinator will thank the candidate and provide her with a list of local resources.

After informed consent has been obtained, the project coordinator will assign the participant a study ID. This study ID will be used for the entirety of the study to identify the participant. The master list that stores the study ID and participant information will be stored in the lead project coordinator's password protected computer in a password protected file.

Participants will complete the baseline assessment upon consent.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

In this study, the enrollment date will be the date that all of the screening criteria were met, and the individual consents to participate.

Baseline Assessments

Participants will complete the baseline assessment upon consenting to participate in the study. The project coordinators will administer the baseline assessment to the participant through a secure online survey. For participants who do not wish to complete the survey online, the project coordinator will arrange for either a phone interview with the participant to complete the survey or will mail the participant the survey along with a self-addressed and stamped envelope for the participant to return the survey. Both forms of the assessment will be coded with a unique study ID.

Randomization

Following baseline completion, participants will be randomized to condition by the lead project coordinator. The lead project coordinator will meet via phone with participants assigned to the MMORE condition to explain the condition. Participants in the MMORE condition will receive a secure password-protected access to the digital companion features.

Randomization will be conducted via permuted blocks. Once 8-10 participants have enrolled, an intervention will commence for that cohort. The randomization block size would be random, with blocks of size 4, 6, and 8. In thinking about how best to implement our group randomization plan in the context of the reality of recruitment of this high-risk target population, we have developed a plan of ongoing recruitment and starting a new group at least every 8 weeks. With a conservative recruitment

rate of 12 participants per month, we do not anticipate a good deal of differential lag-time between recruitment into the study, completion of baseline, randomization, and start of a new group.

6.2.3 Blinding

The study will be blind to the Principal Investigator, the statistician, and to those on the team responsible for participant data collection. We will work to try to blind clinicians delivering TAU to participant assignment but there is a chance that patients will reveal their condition to clinicians despite our best efforts. To achieve blindness, treatment assignment will done by the lead project coordinator, who will not be directly involved in evaluation or data collection. Survey data collection will be conducted by the project coordinator who will be blinded to participant treatment assignment. Participant self-report surveys will be implemented using secured online survey software, which will significantly limit the potential of the project coordinator to introduce bias.

Stakeholder	**Blind Status**	**Involved in Data Collection?**	**Steps to ensure blindness**
TAU Clinicians	Potentially un-blinded	No	Patient participants may indicate to their clinician that participating in study. Clinicians will be instructed not to specifically ask patients about study.
PI	Blinded	No	The PI will not be involved in the group assignment or collection of data; analyses will be conducted when data are unlocked.
Statistician	Blinded	No • Will conduct analyses	Will not have access to randomization algorithm key
Project Coordinator	Blinded, with possibility of being inadvertently un-blinded	Yes	• Will be instructed not to inquire with participants about study. • Will report instances of learning status • Assessments conducted via secured online survey software.
Lead project coordinator	Un-blinded • Knows random assignment • Introduces participants to their treatment condition	No	

	• Prepares necessary reports		

6.2.4 Contamination

Since the study is not necessarily blind to participants, we will take steps to evaluate potential contamination with regard to the intervention by way of communication among women who may receive services in the same setting. It is possible that participants that receive MMORE will interact with women in the TAU only group through the partner practice and communicate about the intervention. While it is unlikely that communication will convey substantive information to influence results, we will evaluate extent of potential contamination by including questions about communication with others about the intervention in the post-intervention assessment battery (e.g. Did you talk with other women in the study? What information conveyed? What information learned?).

6.2.5 Follow-up Visit

All study participants will be followed until 3 months postpartum.

6.2.6 Completion/Final Evaluation

The study team will evaluate intervention implementation outcomes at each of the partner practices to inform exploratory Aim 3 goals of the MMORE intervention at partner practices. In addition to summative indicators of intervention acceptance, feasibility, fidelity, and reach, practice stakeholders will complete indicators of Readiness to Implement Change and Program Sustainability. Descriptive statistics will be used to identify key facilitators to sustained implementation of the intervention.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Procedures to Ensure Safety: All participants will be informed that information obtained through activities is confidential and that they can choose not to answer certain questions. All audio recordings of interviews will be destroyed after transcription. All potential risks associated with participation in this study will be disclosed in consent documents. As in other studies with this population, we have obtained a waiver of signed consent for study activities.

Procedures for minimizing risk to physical health from yoga practices.

Intervention Instructors will complete the Session Event Checklist after each intervention session to denote any adverse events (non-serious and serious) that take place during the intervention sessions. Participants will complete the Intervention Experience Form at the end of each session to document experience of any adverse events including physical experiences (e.g., shortness of breath, pain, increased or decreased infant movement, or other discomfort experiences during the session) and psychological experiences (e.g., emotional flooding, uncontrollable crying). At the end of each intervention week, all participants will also complete a Weekly Monitoring Form that will include items related to any additional experience of adverse physical or psychological events. The lead project coordinator will administer the Weekly Monitoring Form by telephone or e-mail.

Intervention sessions will be conducted at the partner practice. In the event of an adverse physical health event occurring during an intervention session or during the study period outside of intervention session, the instructor and study team member will follow the best practice procedures of the partner practice. Risks associated with physical health will be overseen by Drs. Lord, Goodman and Frew.

The events will be reported, monitored and tracked as outlined in the DSMP.

Procedures for managing suicide ideation or other mental health conditions

As with other interventions, yoga and other mindfulness interventions can elicit feelings for some participants that are uncomfortable. The safety checklists described above will include items related to the experience by participants of emotions or feelings, from quiet tears to sobbing. The experienced Lead yoga instructors in this project are seasoned in supporting clients in managing of feelings so that they do not become overwhelming. The Lead Instructor has worked with vulnerable populations like those in the proposed study, including women with significant trauma histories and involvement in the criminal justice system.

In the unlikely event that participants indicate either during the intervention or in the assessment that they have feelings of hurting themselves or others, the intervention instructor and study team will follow the best practice procedures of the partner practice and the participant will be provided with appropriate referral to treatment and resources. Risks associated with mental health conditions will be overseen by Drs. Lord and Frew.

The events will be reported, monitored and tracked as outlined in the DSMP.

Procedures for managing relapse.

In the event that a study participant lapses or relapses during the study period, cases will be handled on an individual basis, which will be largely determined by the procedures of the partner maternity care practice in terms of preference for ongoing care. A lapse/relapse will not necessarily lead to participant discontinuation in the study.

The lead instructor is trained to manage such instances and the safety protocol to be followed by the instructor and study team will include procedures consistent with partner practices to address situations where discomfort requires a higher level of attention. If a participant is deemed to be impaired at an intervention session such that she is disruptive to the group or presents as a safety hazard to others, the study team member will follow partner practice best practice to work with the participant to leave the room.

Risks associated with substance use and relapse will be overseen by Drs. Lord, Goodman and Frew.

Other procedures to ensure safety, privacy and confidentiality of participants

All efforts will be made to encourage trust and respect among participants in the group sessions and to ensure that information disclosed remains confidential. Any recordings of sessions will use processes to de-identify individual participants. All recordings will be destroyed at the end of the study after processing.

Protection of risks associated with use of a computer or mobile phone to complete research activities. All efforts will be made to ensure data security while utilizing Zoom for the virtual intervention. End-to-end encryption settings will be enabled for an added layer of application security in addition to being password protected with ‘waiting rooms’ enabled, in-progress meetings being locked, and enabling the removal of attendees. The greatest risk with using any virtual platform is entry of

someone other than designated study participants. The Dartmouth institutional Zoom has a number of protections in place, including study staff control of who enters the intervention space (via waiting room and specific participant codes). Per Zoom documentation: "Meeting hosts can enable the end-to-end encryption setting to their meetings for an added layer of application security. Enabling this setting will force encryption across Zoom running on desktop, mobile and Zoom Rooms, as well as for H.323/SIP endpoints except PSTN telephone. It will also force end-to-end group messaging (chats). Dartmouth ITC Security recommends that meeting hosts enable the added layer of end-to-end security for meetings where highly-confidential or regulated information, such as PHI, HIPAA, PII, or FERPA data may be exchanged or discussed." We will be working with Dartmouth ITC to ensure our Zoom platform for virtual delivery is maximally secured technologically.

Participant access to assessment surveys will require unique user login and password, and loss of passwords will require double authentication. Other steps to protect confidentiality include: 1) Mobile phones used in the study will be required to have passcodes to help protect from unauthorized access to the application, 2) Assessment data will be encrypted and secured thus mitigating or reducing the risk of data loss during the transmission process, and 3) Access to the digital support resources of the intervention will also require a unique username and password.

Participants will be instructed that their responses to assessment surveys are voluntary and that they can decline to answer any questions that they choose. They will be assured that participation will not affect their access to treatment or perinatal care in any way.

All data collected will be housed on a secure, encrypted server protected behind firewalls and located in a secured location under 24/7 surveillance. The study team uses state-of-the-field Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering of data while it is in the transmission pipeline. All research assessment data will be stored in secure databases that will not directly link participant data with identifying participant records. A separate, secure database of study participants contact information will be created to assure intervention delivery to enrolled participants and to maximize security. All possible safeguards will be taken to prevent disclosure of personal information; communication of identifiable sensitive personal information via text messages will be avoided. Participants will be instructed not to share their mobile phones.

Confidentiality training will be required for all new employees and project members and refresher seminars annually for all employees. All research staff will fulfill the educational requirements set forth by the Office for Human Research Protections at Dartmouth College. Data for all participants will be kept strictly confidential, except as mandated by law. We have received a Certificate of Confidentiality for the study to further protect participants. Paper documentation will be kept in locked file cabinets located in a locked study team office. All data presentation will be of aggregate-level data; participants are never individually named.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Safety parameters will be assessed by the methods described above and in the DSMP, including the checklist forms and study team member progress notes. The study team will review safety parameters weekly during the course of the intervention. Events will be summarized and provided in a report

provided to the Independent Monitoring Committee. The summary reports will also be reviewed by the SAC.

7.3 Adverse Events and Serious Adverse Events

The potential for unexpected events in this study is minimal. The primary unexpected event may be discomfort when completing assessments that include measures about substance use, stress and mental health, parenting, and recovery. As noted previously, we will take precautions to ensure messages for participants to reinforce the confidentiality of assessment survey, and intervention that participants can take as many breaks as needed when completing study activities. Any other unexpected or adverse events will be handled according to the policies and procedures at our community partners' facilities. These procedures will be summarized and provided to participants at the time of consent.

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

7.4 Reporting Procedures

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on a quarterly basis by way of inclusion in the reports provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

The Contact PI will be responsible for determining whether an SAE is expected or unexpected and related to the intervention. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

The details of reporting and follow-up for adverse events are included in the **Data Safety and Monitoring Plan** for the study.

7.5 Follow-up for Adverse Events

All Adverse Events will be followed in timely manner and consistent with the standard procedures of

our partner practices. AE will be followed for 7 days following the completion of the study period. SAE will be followed for 30 days following completion of the study period.

7.6 Safety Monitoring

The NCCIH requires that all Human Subjects research studies undergo independent monitoring, and NCCIH Program Officials will provide specific guidelines to the PI for the study.

We have identified three independent monitors for the R33 study and their materials have been provided to the study Project Official.

The following safety characteristics will be tabulated monthly and reported to the Independent Study Committee quarterly.

1. Non-serious and serious adverse events, as documented in the Session Event Forms, Intervention Experience Forms, the Weekly Monitoring Forms, and study team member progress notes during intervention sessions. These include physical side effects of the intervention or injuries occurring in class or during home practice.
2. Any other unrelated, possibly related, and related adverse events reported by participants
3. Attribution of adverse event to the study intervention, determination of whether the adverse event was expected or unexpected, and resolution or study adjustments, as necessary

8. INTERVENTION DISCONTINUATION

The research team has the right to ask any participant to leave an intervention session or to discontinue participation in the study to protect the safety of the participant or others in the study.

Reasons that a participant would be asked to leave an intervention session or discontinue participation include:

- Attending sessions or visits impaired or inebriated
- Behaving in ways that are disruptive to others or endanger safety
- It no longer becomes physically safe for a participant to continue in the study.
    - One Serious Adverse Event clearly indicated to be related to the intervention OR
    - More than 3 non-serious AE indicated to be related to the intervention and not reasonably remediable.
    - Participants will be discontinued from the study if they experience complications that could endanger their pregnancy or infant.
- The funding sponsor also has the right to stop the study at any time.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Study Type: Interventional
Estimated Enrollment: 150 participants
Allocation: Randomized
Intervention model: 2-group parallel assignment

The study is a randomized, controlled and blinded efficacy trial comparing Treatment as Usual (TAU) to the Mindful Moms yoga-mindfulness intervention as an adjunct to TAU (MMORE + TAU)

The primary outcomes are MOUD treatment retention and opioid abstinence.
Secondary outcomes include frequency and quantity of other substance use, depression, anxiety, stress, mindfulness, pain perception, and quality of life.

Data collection will occur by way of clinical record review and participant self-report. Self-report assessment surveys will be completed at: baseline, post-intervention, and 3 months postpartum.

9.2 Sample Size and Randomization

Sample Size.

Aim 1: For the longitudinal models of binary outcomes (abstinence, retention), assuming a within-person correlation of 0.5, there will be 80% power to detect difference between arms in the proportion retained at the 3 timepoints if the average percentage retained in the TAU arm is 60%, and the average percentage retained in the MMORE arm is 79.2%. Similar power is obtained if the TAU arm has a retention percentage of 70% while the MMORE arm has a percentage of 87% across the three timepoints. In terms of comparing abstinence longitudinally, there will be 80% power to detect a difference between arms in the percentage abstinent at the 3 timepoints if the average percentage abstinent in the TAU arm is 80% while in the MMORE arm is 94%. Power for the comparison of number of weeks abstinent during the 8-week intervention period will be 80% (at the two-sided 0.05 significance level) for differences between arms that are 0.52 times a standard deviation or more. Analyses testing for differences between arms in changes between baseline and 8-weeks, will have 80% power to detect differences that are 0.40, 0.52, and 0.61 times a standard deviation, assuming within-person correlations of 0.7, 0.5, and 0.3, respectively. We will aim to recruit 150 participants to allow for attrition (20%).

Aim 2: For examining mediation/mechanistic effects at the individual-level from longitudinal data via parallel process growth models (paths from treatment assignment to individual-level slope of mediator to individual-level slope of outcome), with 120 individuals, there will be 80% power to detect indirect effects comprised of a small-medium effects of the intervention arm on latent slope of mindfulness (defined as a correlation of 0.25 between variables or equivalently as explaining 6% of the variance in the latent mindfulness slope) and a medium effect of the slope of mindfulness on the slope of the outcome (defined as a correlation of 0.36 or equivalently as explaining 13% of the variance of the outcome). For examining mediation/mechanistic effects at the weekly level, power is less clear. Although DSEM combines aspects of more familiar modeling techniques, it is new and thus limited information is available on determining power for such models. In one set of simulation studies, good model performance was observed for several models differing in complexity for a sample size of 200 individuals with a number of observations per individual ranging from 20-200, and good model performance for all but the most complex models for smaller sample sizes. Thus, with data from 120 individuals contributing up to 8 observations each, we expect to have enough data to accomplish the aim of understanding the mechanisms underlying the intervention effects of MMORE. We will conduct weekly assessments to minimize participant burden. This strategy will still allow us adequate sampling frequency to track changes in outcome measures over the course of treatment. The power

calculations for the mechanistic effects were based on individual-level latent slope variable estimates and are thus not affected by a change to the number of indicator variables for the latent slope variables (reduced from 70 daily assessments to 8 weekly assessments). Power calculations for the dynamic SEM models are approximate and were not specifically based on having daily assessments per individual so will also not change.

Aim 3 is exploratory and not powered.

Treatment Assignment Procedures

Randomization will be conducted via permuted blocks. Once 8-10 participants have enrolled, an intervention will commence for that cohort. The randomization block size would be random, with blocks of size 4, 6, and 8. We plan ongoing recruitment and to start a new group approximately every 8 weeks.

9.3 Definition of Populations

We will use an Intent to Treat model that includes all participants who complete a baseline assessment.

9.4 Interim Analyses and Stopping Rules

No interim analyses of primary and secondary data are planned for this study.

9.5 Outcomes

9.5.1 Primary Outcome

Treatment Retention. Operationalized as adherence to medication for opioid use disorder and retention in treatment over time.

Opioid use abstinence. Operationalized as number of weeks of consistent abstinence from opioids over the study period and continuity of abstinence from one assessment time point to the next.

9.5.2 Secondary Outcomes

Other substance use.

Self-reported frequency and quantity of opioid and other substance use (including alcohol, marijuana, and tobacco) will be assessed with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), aligned with relevant timeframes (baseline: past 6 months, post-intervention and 3 month postpartum: past 3 months).

Mental Health:

Depression will be assessed using the Edinburgh Prenatal and Postnatal Depression Scales, both of which have been used extensively with the target population.

Anxiety will be assessed with the Generalized Anxiety Disorder Scale (GAD-7)[2], a psychometrically sound instrument routinely used in general health care settings.

Stress will be assessed with the Perceived Stress Scale,[3] a psychometrically sound instrument that has been used in other studies of contemplative interventions with pregnant women[4-7].

Posttraumatic stress will be assessed with the abbreviated PTSD Checklist (PCL-5), a screening instrument developed for primary care and other general medical settings.[8]

Mindfulness. Mindfulness will be assessed with the Mindful Attention Awareness Scale.[13] This instrument has been used with demonstrated strong psychometrics in mindfulness intervention studies with pregnant women[4] and substance using populations[9-12]. *Acceptance* will be measured with the Acceptance and Action Questionnaire (AAQ), which has been used in other mindfulness studies with substance-using populations[9,12].

Quality of Life. Quality of life will be assessed with the World Health Organization QoL BRF, a widely used instrument with demonstrated validity and reliability with pregnant and early postpartum women.

Pain Perception. Pain Perception will be assessed by a widely used visual analog scale (VAS) used in other studies with pregnant women. Participants report point areas and levels of pain on a scale from 0 (no pain) to 10 (worst possible pain) and anchored with descriptive faces.

9.6 Data Analyses

Aim 1
Primary analysis: The difference between treatment arms with respect to likelihood of opioid abstinence and remaining in treatment will be evaluated by logistic generalized estimating equations (GEE). Since these binary outcomes will be evaluated at the 8-week as well as the 3-month postpartum time points, these GEE models will account for the non-independence of repeated measurements within individual. An indicator of treatment arm, time point, as well as an interaction between treatment and time point will be included as predictors in the model along with baseline covariates. Significant differences between the arms will be tested via contrasts involving the treatment*time point interaction term that compare the outcomes at each time point.

The impact of *MMORE* on treatment retention (number of weeks retained) will be evaluated via two-sample t-test if the distribution appears symmetric, but a non-parametric Wilcoxon rank sum test will be used otherwise.

Aim 2.
Primary analysis: Analyses of mechanisms of effect of *MMORE* will be performed via parallel process growth models fit via structural equation models, and mediated effects between treatment assignment and outcome will be examined for the following mediator-outcome pairs: craving-abstinence, mindfulness-craving, mindfulness-treatment retention, depression-treatment retention, anxiety-treatment retention, stress-treatment retention, and mindfulness-pain. Since each mediator and outcome variable will be collected at multiple time points, latent intercept and slope effects can be estimated (as in latent growth curves). The parallel process growth models then examine mediation of the effect of an individual-level variable (treatment assignment) on the latent slope of the outcome variable by the latent slope of the mediator variable. For each mediator-outcome pair, a parallel process growth curve model will be fit including both the direct effect of treatment assignment to *MMORE* on the latent slope of the outcome, as well as the indirect effect of *MMORE* on slope of the outcome through the slope of the mediator. Estimates of path coefficients for each individual path as well as of the indirect effect along with a 95% bootstrap confidence interval will be obtained.

To examine these associations we will implement a newly developed modeling strategy called dynamic structural equation models (DSEM). DSEM like non-dynamic SEM are a modeling

framework that allows for estimating simultaneous sets of equations involving latent and observed variables, thus allowing modeling of multi-level data, and modeling relationships at each level including mediation. Unlike non-dynamic SEM, however, DSEM have the capability to estimate time-series model(s) at the within-individual level, and also allow for a between-time level model (in addition to the between-individual level model) to incorporate time-varying effects observed in intensively collected data (i.e. creating a cross-classified model). Thus DSEM combine the advantages of time-series models, multi-level models, time-varying effect models, and other SEM, and importantly for the current application allows examination of relationships between multiple intensively collected variables (here affective state, mindfulness, stress, and craving) as well as moderation of these relationships by both individual-level (here treatment arm) and daily-level (session attendance, mindfulness) variables. The DSEM is specified by models at three levels. The three-level specification results from a decomposition of the observed variable(s) for a given individual at a given time (vector Y_{it}^{*}) into three latent, unobserved parts: an individual-specific contribution $Y_{2,i}$ a time-specific contribution $Y_{3,t}$ and a deviation for an individual, at a given time $Y_{1,it}$ ($Y_{it}^{*} = Y_{1,it} + Y_{2,i} + Y_{3,t}$). For example, for stress, observed weekly stress ($dStr_{it}^{*}$), becomes: $dStr_{it}^{*} = dStr_{it} + Str_i + Str_t$. These three latent components are then modeled simultaneously in a within-individual, between-individual, and between-time model. The time series describing the relationship between past and current observations in one or more intensively collected variables is modeled at the within-individual level (detailed below) The between-individual model examines influences on mean weekly stress (Str_i) and mean weekly craving as well as influences on individual-level random effects specified in the within-individual model (e.g. $\varphi_{SC,i}$: representing the relationship between weekly craving and weekly stress). The between-time model examines influences on the mean daily stress at a given time (Str_t) and on mean weekly craving at a given time (as well as influences on time-specific random effects specified at the within-individual model). For the current application, one within-individual model is a bivariate autoregressive (here specified with a lag of 1 but other lags will be explored) of weekly stress ($dStr_{it}$) and weekly craving (dCr_{it}).

$$dStr_{it} = \varphi_{SS,i} dStr_{it-1} + \varphi_{SC,i} dCr_{it-1} + \zeta_{S,it}$$
$$dCr_{it} = \varphi_{CC,i} dCr_{it-1} + \varphi_{CS,i} dStr_{it-1} + \zeta_{C,it}$$

We will obtain an estimate of the relationship between the current value of dCr and lagged value(s) of dStr ($\varphi_{CS,i}$). Moderation of this relationship by immediate contextual variables (such as weekly mindfulness value, mindfulness session attendance (among those on MMORE arm)) can be examined by including an interaction between time-varying context variables and dCr in the dStr equation. Since the regression parameters estimated are considered random individual effects, associations with other individual-level variables (such as treatment arm assignment) can be modeled in the between-individual model. This will allow us to examine moderation of the weekly relationship between dStr and dCr by individual-level variables. Mediation of the effect of immediate contextual variables on mRB by mSR will be evaluated using a cross-lagged mediation model.

Aim 3 (Exploratory). Quantitative data will be descriptively summarized, and qualitative data coded for salient themes using standard deductive methods described earlier. Data summaries will be reviewed by the Steering Committee and consultants to inform strategies to support dissemination and sustainable implementation of MMORE in women's health care settings. Data will guide interpretation of participant outcomes.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Opioid abstinence and MOUD treatment retention will be collected by way of medical chart data extraction and self-report by consented participants.

Secondary outcomes will be collected by way of self-report by consented participants through completion of assessment surveys.

Case Report data collection forms have been created for the following:

- Participant Demographics and physical conditions at baseline
- Session Events Form
- Intervention Experience Form
- Weekly Monitoring Form
- Adverse Events
- Clinical Record Data Collection Template
- Self-Report Assessment Battery (SRAB)

The SRAB has been programmed in secured, password protected HIPAA compliant online survey software (Dartmouth College REDCap). Individual participant survey links will correspond to the unique participant study ID so that all pages of each assessment survey (and corresponding database) will be linked to the participant.

10.2 Data Management

Participant data will be coded with unique study identifier numbers with all identifying information removed. Any paper-version surveys will be entered into the secured online system and stored in locked filing cabinets, in locked offices at the Center for Technology and Behavioral Health (CTBH). All data collected on mobile tablets or laptops will be done so via secured online surveys accessed through password-protected links, and data will be stored in secured databases on secure cloud-based servers. The lead project coordinator will have the primary responsibility for securely storing any audio recordings of interviews completed as a part of this study. Recordings, participant data, and de-identified transcripts of interviews will be stored on the research study staff secure and password-protected computers and destroyed after study completion.

10.3 Quality Assurance

10.3.1 Training

Lead Yoga Practitioner Black will train two other highly experienced yoga instructors in the Mindful Moms intervention using the training materials and manual developed in first year of the project.

10.3.2 Quality Control Committee

We have identified three independent monitors for the R33 study and their materials have been provided to the study Project Official.

10.3.3 Metrics

Intervention sessions will be video and audio recorded to allow for evaluation of fidelity over the

course of the study.

The study team will review data weekly to ensure quality and completeness.

The study data engineer will develop and maintain the database and prepare the dataset for analyses.

10.3.4 Protocol Deviations

All intervention protocol deviations will be clearly denoted on the *Session Events Form*.
All research study protocol deviations will be clearly denoted on *Protocol Deviations Form*.

10.3.5 Monitoring

Data accuracy and completeness will be monitored by the lead project coordinator.

The Independent Monitors will also receive quarterly summaries of study progress, recruitment and retention indices, and any adverse events.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and associated documentation has been submitted to the Dartmouth College Institutional Review Board for approval.

11.2 Informed Consent Forms

We adapted the IRB-approved consent form for the R21 Pilot Study for use in the R33 phase study. The consent forms describe the overall nature of the study, the potential risks and benefits, and the study activities and incentives for participants.

11.3 Participant Confidentiality

A Certificate of Confidentiality has been obtained for this protocol.

All efforts will also be made to protect confidentiality in the context of the Mindful Moms Intervention sessions. Only first names will be used. Participant access to the mobile prototype components of the intervention and online assessment surveys will require unique user login and password, and loss of passwords will require double authentication. Assessment data will be encrypted and secured thus mitigating or reducing the risk of data loss during the transmission process. All study assessments will be coded with a unique study ID. We will not collect personally identifiable information in the research database.

All data collected will be housed on a secure, encrypted cloud server. Data will be collected using current state-of-the-field Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering of data while it is in the transmission pipeline. All assessment data will be stored in secure, password protected databases that will not be directly linked to participant identifying information. A separate, secure database of study participants contact information will be created to maximize security. All paper documentation will be kept in locked file cabinets located in a locked study team office. All possible safeguards will be taken to prevent disclosure of personal information, including during any communication with participants (we will NOT use text messages to participants). Participants will be instructed not to share their mobile phones.

Confidentiality training will be required for all new employees and project members and refresher

seminars will be offered annually for all employees. All research staff will fulfill the educational requirements set forth by the Office for Human Research Protections at Dartmouth College. Data for all participants will be kept strictly confidential, except as mandated by law. All data will be presented in de-identified, aggregate formats.

11.4 Study Discontinuation

The institutional IRB, the NCCIH, the OHRP, the FDA, or other government agencies may discontinue the study at any time as part of their duties to ensure that research participants are protected.

12. COMMITTEES

We have created a Steering Committee for the study that includes NH stakeholders as well as MOUD and maternity care clinicians, and women with lived experience. The Steering Committee has reviewed study materials and provided input on the Mindful Moms intervention.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. The investigative team will make presentations, abstracts, and manuscripts available for review by the sponsor and the NCCIH prior to submission.

14. REFERENCES

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15. SUPPLEMENTS/APPENDICES