PROTOCOL: MOms in REcovery (MORE): Defining optimal care for pregnant women and infants.

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BACKGROUND

Opioid-related overdose is a leading cause of maternal mortality in the United States overall, and northern New England in particular. Medication treatment for opioid use disorder (MOUD) with methadone, buprenorphine or naltrexone, combined with group or individual counseling, is the recognized standard of care during pregnancy.[1-8] Professional societies, including the American College of Obstetricians and Gynecologists,[9] the American Academy of Pediatrics,[10] the Society for Maternal-Fetal Medicine[11] and the American Society for Addiction Medicine[4] call for improved access to MOUD treatment for pregnant women/birthing people with Opioid Use Disorder (OUD), but questions persist regarding the optimal approach to providing MOUD. For the past 30 years, the primary strategy has been to refer pregnant women to specialty MOUD programs. However, in response to an escalating crisis, a growing number of obstetric providers now integrate MOUD into existing maternity care services,[13,14] along with a variety of psychosocial and other services, and Northern New England's high rate of OUD among pregnant people and state efforts to increase MOUD access resulted in a large number of maternity care practices beginning to offer MOUD services, providing a rich opportunity to compare the effectiveness of integration of MOUD with prenatal care versus referring pregnant patients with OUD to specialty MOUD programs for treatment [**RQ-1**]. Regionally, maternity care practices fall into two broad categories: (1) Integrated care, defined as the provision of maternity care, MOUD, and/or varying psychosocial services, and care coordination together in the same practice, and (2) Referral-Based care in which maternity care is provided at one location, and pregnant patients are referred to community-based providers, distinct from their maternity care providers, for MOUD treatment; in this model, psychosocial services might be provided at either location. Within these two categories, the type of psychosocial services offered and level of care coordination available might vary. Within the "integrated" model, either integration of MOUD treatment into a prenatal care providing practice or integration of prenatal care into an MOUD-treatment providing context were included. Due to federal rules restricting the location of methadone treatment/dispensing, an integrated approach to providing methadone with prenatal care was not available in these northern New England states, although pregnant people were able to access integrated prenatal programs for other

aspects of their perinatal and/or substance use care **[RQ-2].** The MOms in REcovery (MORE) study directly compares real-world effectiveness of Integrated vs Referral-based models of MOUD with respect to patient reported outcomes and experience of care and perinatal, neonatal, and substance use treatment outcomes, with two primary Specific Aims:

Aim 1 (Retrospective: Clinical Outcomes): Use clinical record data to evaluate comparative effectiveness of Integrated and Referral-based MOUD care models on maternal and neonatal outcomes. **[RQ-5]**

Aim 2 (Prospective: Patient-Reported Outcomes): Use prospective patient-reported data to evaluate the comparative effectiveness of Integrated and Referral-Based MOUD care models on patient-centered outcomes. **[PC-3]**

Methods

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

Our commitment to patients and clinical, administrative, and policy-maker stakeholders was fulfilled by involving them in every step of research, starting with development of the research questions on which the MORE study was based, through engagement in the Study Advisory Committee (SAC) throughout the duration of the study, development of study measures and recruitment strategies, and in the analysis of qualitative data and dissemination activities. Our engagement plan was guided by principles of participatory action research that are critical to the successful conduct of patient-centered outcomes research[14] in the following material ways:

(1) Promoting reciprocal relationships by fostering shared leadership on study processes: A robust Study Advisory Committee was convened, representing the diverse range of patients and stakeholders impacted by perinatal OUD, immediately after the study was funded. Our Study Advisory Committee (SAC) engaged patients, clinician stakeholders and policy makers in providing guidance for the design of the study overall. The SAC met twice annually for the duration of the study, providing opportunity for the sharing of perspectives across disciplines, roles, and lived experiences. Consistent with participatory action research and co-production best

practices, our governance structure supported shared power and collaboration. The SAC was co-led by a patient partner and stakeholder who facilitated each meeting. Study governance structures that enabled this deep level of engagement are described in our recent publication, written collaboratively with the SAC.[16] [PC-1]

(2) Building trust by recognizing individual competencies, acknowledging contributions, encouraging open dialogue and questions, and ensuring transparency and honesty by fostering open channels of communication and making all aspects of the study accessible and replicable: SAC members with lived experience were deeply involved in all aspects of the study, developing procedures, giving feedback on recruitment and consent processes, actively engaging with potential participants to introduce them to the study, contributing to refinement of quantitative assessment surveys and co-creating interview guides, and participating in qualitative data analysis and dissemination. Active participation of the SAC ensured study relevance, data integrity, meaningful interpretation, and broad opportunity for dissemination. [PC-1,3,4]

(3) Fostering partnerships through agreement to advance mutual interests from the onset of the study: SAC workgroups met weekly to biweekly throughout the study duration to discuss study progress and potential challenges. During the height of the COVID pandemic all meetings were conducted via Zoom.

(4) Providing opportunities for co-learning and sharing of experiences and expertise: SAC members with lived experience completed Collaborative Institutional Training Initiative (CITI) research ethics and community engagement training programs, participated in methods training and contributed to deep discussion about study methods and implications for data analyses and interpretation [PC-1, PC-2]

To honor our research partnership, our team (researchers and SAC members with lived experience) met for a final SAC appreciation gathering in June 2023. At this meeting we made a commitment to work together to disseminate MORE Study findings and to build on the study with future PCOR/CER. Consistent with recommendations of participatory action researchers[18],

SAC members completed a survey to evaluate group dynamics related to SAC functioning. Our plan aligned with PCORI Engagement guidelines and implementation science frameworks[19,20].

In addition to the deep involvement of people with lived experience of pregnancy, parenting and OUD, our research team also included other stakeholders who participated in multiple aspects of the study. The chart abstraction team (Main Study, Aim 1) was made up of key clinical stakeholders, the majority (3/4) of whom were Registered Nurses with many years of experience in maternity care and caring for pregnant people with OUD. This participatory research lens provided a depth of understanding of the subject matter to their data collection, enabling a level of data quality that would otherwise have been difficult to achieve. The expertise of this group was also tapped in co-creating the data codebook and data abstraction process and participating in qualitative analyses and manuscript and poster preparation.

Additional benefits to engagement. The SAC workgroup became a very important connection for women with lived experience, who frequently spoke about how participating in the study both validated their experiences and perspectives and helped them feel that their own journeys through recovery could benefit others. SAC members with lived experience expressed that the study impacted both their self-esteem and life trajectory, including a sense of purpose. This, in turn, was confidence building. Most who first joined the SAC were unemployed/seeking employment; most have now obtained a part- or full-time job. The trust relationships developed between the Study Team and SAC members have resulted in ongoing collaborations, including participation in state and local initiatives and in research projects advocating for improved care and treatment access for people with substance use conditions.

The study provided a sense of community and network not only for SAC members with lived experience of pregnancy and OUD but also for study participants. Participation was described by some as “empowering”; rather than feeling as victims of a system that often felt biased against them, they were being asked to share knowledge and expertise about their experience. Many asked to be included in the distribution list for the study newsletter and/or the study website or social media; some have stayed in touch through these mechanisms. Many participants indicated interest in being contacted for future research studies. Ultimately,

the experience of this collective study team (research staff and SAC) has been transformative. Study staff expressed a sense of humility and appreciation for working with SAC members with lived experience and acknowledged how much they have continued to learn from them.

Connecting through hard times. Over the course of the study the SAC team also experienced the tragic loss of two SAC members, unrelated to study activities. This was extremely difficult for the entire research team, many of whom attended their memorial gatherings together. To make sure they were always remembered as part of the study team, their names and pictures were subsequently highlighted at all SAC meetings and presentations.

Participating Practices

Aim 1 (Retrospective: Clinical Outcomes): We partnered with 26 practices that provided maternity care to pregnant people with OUD throughout the northern New England catchment. Of these, 23 sites contributed records for abstraction; others were constrained by institutional and/or logistical constraints. Partners represent federally qualified health centers, family practice settings, and public and private obstetrics and gynecology practices. Practices served a wide range of volume of pregnant people annually, from less than 100 through well over 1000 in larger urban sites. These practices were roughly evenly proportioned for Integrated (11) and Referral models (12). **[IR-2]**

Aim 2 (Prospective: Self Report Outcomes): Partner practice settings included our original 26 maternity care practice partners who had participated in formative work with the team to inform and prepare for the project proposal submission. These settings were part of the Northern New England Perinatal Quality Improvement Network (NNEPQIN). An additional 42 maternity care settings were added to improve achievement of our recruitment goals, which were significantly slowed by the multi-year impacts on research and clinical care during and following the COVID pandemic. These additional sites were recruited through community outreach conducted by the project research staff. Each site was designated as Integrated or Referral based on research staff communication with the setting practice manager as meeting criteria (e.g., Integrated: medication treatment (buprenorphine) for OUD part of the practice service menu; Referral: medication treatment not part of the practice service menu). The 68

settings collectively represented rural, suburban, and urban regions of our catchment area (ME: n=27, NH: n=33, VT: n=8). Roughly one third of sites in Maine were designated Integrated (Integrated:10/Referral:17). Sites in NH were roughly balanced (Integrated:17/Referral:16); and sites in VT were primarily Referral (Integrated:2/Referral:6). Partners represented community health/federally qualified health centers, family practices, and public and private obstetrics practices. Overall, 28/68 recruitment settings represented our operationalized Integrated care model; 40/68 settings represented the Referral model.

Participants

Aim 1. Eligible records reflected pregnant and postpartum people with a diagnosis of OUD and/or who were treated for OUD, who delivered between September 1, 2015 and December 31, 2022. Records were identified through a standardized set of ICD-10 codes utilized for perinatal substance use and OUD and pregnancy identifiers that were iteratively validated through prior research[21] by the team and deployed to query electronic medical records systems for eligible cases. **[IR-1, IR-2]**

Aim 2. Participants were pregnant women aged 16 years and older with an identified OUD, receiving prenatal care, and with demonstrated ability to provide informed consent. Pregnant women under 18 years of age were included per PCORI request. A waiver of parental consent was granted from the Dartmouth Committee for Protection of Human Subjects.

Interventions and Comparators or Controls

Aims 1 and 2 compared the two maternity care models (Integrated and Referral) on clinical and self-report outcomes. Integrated care was operationalized as MOUD provided as part of the maternity practice service menu, and Referral-based care operationalized as the maternity setting not offering MOUD as part of service menu and having a standard practice of referring patients out to specialty care or community providers for MOUD. All participants were anchored to the date at which they initiated prenatal care, ensuring that potential impact of change of care model on results, if any, was negligible.

Methods

Aim 2 (Prospective: Self Report). Aim 2 was specifically designed to prospectively follow a cohort of pregnant women with OUD from pregnancy to 6 months postpartum to

examine comparative effectiveness (CE) of the two care models on patient-reported outcomes, including MOUD retention, mental health, perceptions of care, quality of life, and retention of child custody. Patient reports of their care experiences can provide important depth of information to complement clinical data. Following participants to 6 months postpartum allowed us to evaluate the association of care model for the important early postpartum months, when the literature has consistently demonstrated a drop in treatment retention for women with OUD.[25,26] Surveys with participants occurred at 3 time points: 3rd trimester pregnancy, and 3- and 6-months postpartum.

Outcomes

Aim 1 Primary Outcomes:

MOUD Treatment, defined as receiving MOUD (yes/no) in the 3rd trimester, at the time of birth hospitalization, and at 6 weeks post birth and operationalized through medication lists, positive urine screen (methadone, buprenorphine, naltrexone), and/or provider notes;

Perinatal complications, operationalized as a dichotomous variable (yes/no)) based on documentation of any of the following conditions in the antenatal period: pre-eclampsia, fetal growth < 10% intrauterine growth restriction, miscarriage, fetal demise, antenatal bleeding, placental abruption, and deep vein thrombosis. We excluded diagnoses specifically defined as severe maternal morbidity because these typically occur during or after birth. These latter diagnoses, defined according to ICD 10 codes[22] were captured separately;

Non-prescribed opioid use, defined as documented presence (yes/no) of any opioid (fentanyl, heroin, oxycodone, etc) in urine toxicology at birth hospitalization;

Aim 1 Secondary Outcomes:

Other substance use, defined as dichotomous variable (yes/no) based on presence of positive urine toxicology for any of the following at delivery: barbiturate, bath salts, benzodiazepine, cannabinoids, cocaine, ethanol, kratom, methamphetamine

N**eonatal complications**, operationalized as a dichotomous variable (yes/no) if any of the following were documented: Birth weight <=2500 gm, Apgar score < 7 at 5 minutes, Apgar score <7 at 10 minutes, neonatal complications (not related to Neonatal Opioid Withdrawal Syndrome (NOWS)/Neonatal Abstinence Syndrome (NAS)), or other medical problems.

Pharmacologic treatment for NOWS/NAS, dichotomous variable (yes/no) based on record indication of newborn treated with a pharmacologic agent due to withdrawal symptoms.

Aim 2 Primary Outcomes

Medication treatment for OUD: Single item at the three timepoints ("Are you currenting on medication for opioid use disorder? yes=1/no=0). Those who responded affirmatively received follow up questions regarding when they **initiated MOUD**, the **type of MOUD** received (1=methadone, 2=buprenorphine, 3=naltrexone) and **where they receive MOUD** (1=where receive prenatal care, 2=specialty care or community provider).

Depression symptomatology was assessed at each time point with the Edinburgh Prenatal/Post Natal Depression Scale.[27] This 10-item measure has been used extensively with pregnant and parenting women, including those with substance-use conditions, and has strong psychometrics for women in both prenatal and postnatal periods.[28,29] Total scores were computed based on scoring guidelines (range: 0-30). A binary variable was created based on established clinical cutoffs: Low (0): score <= 13, none to mild depression symptoms/High (1): score >13, moderate to severe symptoms).

Anxiety symptomatology was assessed at each time point with the 7-item Generalized Anxiety Disorder Scale (GAD-7), which has been used in studies with substance use populations.[30,31] Total scores were computed based on scoring guidelines (range: 0-21). A binary variable was created based on established clinical cutoffs: Low (0)= score <= 10, none to mild anxiety symptoms/High (1): score > 10, moderate to high anxiety symptomatology.

Perceptions of Care was assessed in the 3rd trimester of pregnancy with the 28-item Experience of Care module of the Consumer Assessment of Healthcare Providers and Systems (CAHPS) Clinician and Groups Survey, modified to reference prenatal care specifically.[32] A total score was created by averaging the items on the 5-point response scale, with high scores indicative of more positive patient-centered care perceptions.

Aim 2 Secondary Outcomes

Quality of Life was assessed with the 28-item WHOQOL Bref, a well-established and frequently used instrument in health services research, including with substance use affected populations.[33,34] Items reflect 4 domains: Physical (7 items), Psychological (6 items), Social (3 items), Environment (8 items). Individual QOL domain scores were created per the scoring protocol (range: 0-100).

Retention of Child Custody was assessed with a single item, "Do you currently have custody of the child you most recently gave birth to?" (1=Yes Custody/0=No custody).

Scheduled Pediatric Visit Adherence was assessed with a single item at 3 and 6 months postpartum ("In the past 3 months, has the child you most recently gave birth to attended scheduled pediatric care appointments?"). A binary variable was created (1=Yes/0=No).

Moderators. For the planned heterogeneity of treatment effect analyses (Aim 3), type of medication for OUD (methadone/buprenorphine) was collected for participants receiving MOUD. Past year opioid use addiction severity was assessed at 3rd trimester using self-report of the DSM-5 criteria for opioid use disorder.[35] Scores of 6 or more reflect severe disorder. A binary variable of opioid use severity was created (0=low severity, 1=high severity).

Covariates included sociodemographic characteristics demonstrated in the literature or through clinical experience to be associated with the target outcomes or to potentially impact where pregnant persons received prenatal care. Covariates included participant age, race, ethnicity (Hispanic/non-Hispanic), employment (employed/not employed) and highest level of education (high school equivalent or below/more than high school) , relationship status (partnered/not partnered), whether first pregnancy (yes/no), extent of polysubstance use (frequency of regular co-occurring substance use), extent of opioid use severity (count of opioid use disorder symptoms per DSM V), insurance status (insured/not insured), housing stability (stable/not stable), and travel time to get to their maternity care setting (30 minutes or less/more than 30 minutes). State was included to account for imbalance of care models across states.

Data Collection and Sources

Aim 1. Eligible records reflected pregnant and postpartum people with a diagnosis of OUD and/or who were treated for OUD, who delivered between September 1, 2015 and December 31, 2022. Records were identified through a standardized set of ICD-10 codes utilized for perinatal substance use and OUD and pregnancy identifiers that were iteratively validated through prior research[21] by the team and deployed to query electronic medical records systems for eligible cases. De-identified records were abstracted by trained nurses using a clear template for recording data.

Aim 2. Data collection occurred from March 2020-December 2023. We defined our sampling framework as enrollment of eligible participants upon initiation of prenatal care, with first data collection at 30-36 weeks gestational age (3rd trimester) and follow-up at 3 and 6 months postpartum. This framework allowed for uniformity of data collection, sufficient exposure to a given care model, and evaluation of impact on outcomes across the postpartum period.

Assessment surveys were developed in the Dartmouth College HIPAA-compliant REDCap survey software. Participants who preferred or could not complete surveys online could complete surveys by phone with study staff or a paper version that was then input into the survey software by study staff. The survey included indicators of sociodemographic characteristics (maternal age, race, state residence, ethnicity, education and employment status, insurance status, housing stability, travel time to

prenatal care setting) as well as outcomes and associated covariates. The surveys also included indicators of posttraumatic stress disorder, intimate partner violence, recent substance use frequency, social determinants of health, adverse childhood experiences, health services utilization, perceived parenting confidence, and resilience. Survey drafts were refined by the SAC members for wording, clarity, flow, and usability of the online survey system. Participants who completed surveys were compensated with gift cards of their choice (3rd trimester: $55; 3 months postpartum: $75; 6 months postpartum: $150). Participants received a $100 bonus for completion of all 3 surveys (total possible incentive: $380). The following indicators and instruments were used to assess primary and secondary outcomes and planned moderators.

Sample Size Calculations and Power

Aim 1 Retrospective. The retrospective sample included records from 2070 pregnancies of women with OUD. Since this sample was drawn from records, there was no attrition. Although there were missing values for some covariates and outcomes we met or exceeded the anticipated effective sample size of 1720 After adjusting for practice-clustering effects. Assuming two-tailed tests of statistical significance and alpha set at .01 to control for multiple tests we were more than adequately powered (99%) to detect small effect sizes (0.09 to 0.12 difference in proportions, and the corresponding odds ratio ranges from 1.47 to 1.61.) for both primary and secondary AIM 1 outcomes. Note that both primary and secondary outcomes were analyzed after propensity score adjustment, which reduced the original effective sample size from 2,070 to 861 for the Aim 1 data. This reduction primarily resulted from missing values in nine covariates used for the propensity score analysis, as well as the exclusion of extreme probability-of-treatment values to obtain a stabilized propensity score. Despite the reduced sample size (N = 861), we still have 90% power to detect a proportion difference of 0.13, corresponding to an odds ratio of 1.67. This is equivalent to Cohen's h (for a proportion outcome) of 0.28, which is close to the small effect size threshold of 0.20 in Cohen's h metric. This result is based on a two-tailed test with an alpha level of 0.01 and an adjustment for 23 sites.

Aim 2. Sample size was calculated for baseline (3rd trimester), n=523 pregnant persons with OUD. We expected 20% attrition by 3 months postpartum (n=418) and 30% by 6 months (n=366). Adjusting for practice-cluster effects, we expected an effective sample size of 352 at 3 months (176 per each care model condition) and 314 (157 per each care model condition) at 6 months. Power analyses were conducted based on adjusted sample sizes. Specifying alpha = 0.01, two-tailed test, and correlation between 3- and 6-month assessments of 0.50, this study achieves 80% power to detect a minimum difference in proportions of 0.17, which corresponds to an effect size of 1.98 (odds ratio) for Primary Hypothesis 2.1 (MOUD retention) and Hypothesis 2.2 (Depression, Anxiety). This effect size was between small (1.5) and medium (2.5)

in the odds-ratio metric. For Primary Hypotheses 2.3 and Secondary Hypothesis 2.4, this study achieves 80% power to detect a small-medium effect size D of 0.33. Power was the same for Secondary Hypothesis 2.5.

Analytical and Statistical Approaches

In preparation for model estimate analyses we first used chi square tests of baseline demographics and generated univariate and bivariate models to examine the association between demographics and treatment model. Propensity scores (PS) for treatment models were then developed to balance conditions using inverse probability of treatment weighting (IPTW) method.[36,37] We selected nine relevant baseline demographic and clinical covariates (age, birthing person's race, ethnicity, other living children , employment, housing status, marital status at delivery, insurance status in third trimester and education) to compute a propensity score (PS) for each participant using logistic regression. No polynomial or interaction terms were included in the propensity score weighting calculation, as sufficient balance was achieved using the nine predictors. We then computed IPTW from propensity scores using SAS Psmatch procedure. Weights were calculated as 1/PS for participants in the Integrated condition and 1/(1-PS) for the Referral condition. The propensity score modeling yielded satisfactory balance for all covariates, as evidenced by key balance assessment criteria: standardized mean differences falling within the range of -0.25 to 0.25 (Table 3 and plot 1) and substantial overlap in propensity scores between the two care models (plot 2). We did not report other balance assessment measures, such as distributions comparisons for each covariate as most of these covariates were dichotomous, and distribution plots for those covariates are not particularly informative. The outcome analyses were then conducted with the weighted sample.

Aim 1. Outcomes for the primary hypotheses are dichotomous. We used generalized estimating equations (GEE) with logit link functions and binomial distributions to test these hypotheses. The same GEE approach was also used to test secondary hypotheses.

Aim 2. We will first examine baseline differences between participants in the two care models (Integrated vs. Referral) to identify potential sources of confounding due to selection effects. The best practice step process outlined by Austin was used to create and balance propensity scores for the sample using inverse probability of treatment weighting (IPTW).[36] We will use the IPTW approach to best preserve sample size and power for analyses. We will measure demographic and clinical covariates to compute a propensity score for each participant using logistic regression analysis. Covariates include participant race, age, whether first pregnancy, relationship status, housing stability, current employment, education, insurance status, travel distance to maternity setting, and state of residence. IPTW weights will be calculated as 1/PS for participants in the Integrated condition and 1/(1-PS) for the Referral condition. We will check balance of the baseline covariates of the two conditions with the weighted sample weighted using established methods, including comparison of standardized differences before and after weighting.[36-38] Model estimate analyses were then conducted with the weighted sample.

Primary Hypotheses: Compared to women receiving care in Referral-Based practices, women in Integrated practices will: (2.1) have higher rates of MOUD treatment retention at 6 months postpartum; (2.2) have lower depression and anxiety, and (2.3) report greater patient-centered care experiences. To test the first two hypotheses, we will use generalized linear estimating equations model (GEE) with logit link functions, binomial distributions and robust estimation. Group (Integrated vs. Referral-based Condition), Time, and group*time interaction were tested. Time-averaged difference between conditions was evaluated by significance testing of the group effect. GEE with identity link function and normal distribution was used for Hypothesis 2.3

Secondary Hypotheses: Compared to women in Referral-Based practices, women with OUD receiving prenatal care in Integrated practices will: (2.4) report higher quality of life; (2.5) be more likely to maintain child custody relative; and (2.6) report higher rates of recommended pediatric visits. GEE with identity link/normal distribution

will be used to test secondary hypothesis 2.4, evaluating Group, Time, and Group x Time effects. GEE with logit functions/binomial distributions will be used for to evaluate hypotheses 2.5 and 2.6.