Study Protocol

Optimizing Treatment Interventions for Moms 2.0

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1.0 INTRODUCTION

1.1 Background and Significance to the Field

Opioid-Related Adverse Events among Women Persist as a Serious Public Health Problem

The US opioid epidemic continues to result in serious health consequences for pregnant and postpartum women. In the US from 2007 to 2012, an average of 21,000 pregnant women each year reported past month opioid misuse. [1] Age adjusted rates for overdose among women in the US increased more than six-fold from 1.4 in 1999 to 8.5 in 2016.[2] Examining Pennsylvania (PA) and Utah (UT; the states where recruitment will happen in this study), these states have some of the highest rates of overdose among women compared to other US states.[2] Specifically, PA's overdose rate among women surpassed the national average in 2016, and rates of overdose death in UT among women have ranged 2-9 times higher than the national rate between 2009 to 2016.[2] Both PA and Utah are among the states with the highest opioid prescribing to pregnant women, with Utah being the highest in the nation (41.6%).[3] Prenatal opioid use disorder (OUD) in the US has brought serious health consequences for mother and infant—including preterm delivery, low birth weight, NAS, and poor breastfeeding, and includes substantial expenditures of health care resourcs.[4-9] Chances for HIV (OR=20.3, 95% CI = 13.8–29.7) and HCV (OR=150.2. 95% CI = 120.9–186.6) infection among women with OUD are markedly higher than for those without OUD.[10] Pregnant women with OUD have high rates of psychiatric illnesses,[11,12] such as depression and anxiety,[12-16] and other substance use disorders (SUDs),[14,16,17] with particularly high rates of smoking (>80%).[10,14,17] Neonatal abstinence syndrome (NAS), an opioid withdrawal syndrome among neonates, has also increased substantially from 3.4/1000 births in 2009 to 5.8/1000 births in 2012.[18] Poly-substance use among pregnant women with OUD has also been associated with higher levels of needed medications to treat NAS[19] and longer duration of NAS treatment.[20] Smoking combined with opioid use during pregnancy has likewise been related to longer duration of NAS treatment,[21,22] greater NAS severity,[23,24] and higher levels of medication needed to treat NAS symptomology.[21,25] Any prenatal opioid use also has been associated with birth defects, including neural tube defects,[26,27] conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, and gastroschisis.[27] Compared with women without any SUDs, children born to mothers with OUD or OUD plus other SUDs also have been documented to have lower cognitive functioning as they mature.[28] Problems resulting from illicit and prescription OUD also result in significant social issues. Pregnant women with OUD have been observed to have financial and housing instability,[16] challenges related to employment, and involvement with the legal system.[29,30] These data call for rapid and targeted primary prevention activities aimed at assisting pregnant women with OUD to become linked to and retained in treatment in order to reduce harms to them (including overdose) and their offspring. This project will expand our preliminary research of a novel patient navigation (PN) intervention designed to link and retain pregnant women with OUD in treatment (including MAT) and improve the health and wellbeing of mother and infant. [31]

Opioid Use Disorder during Pregnancy is a Treatable Chronic Condition

The National Institute on Drug Abuse defines addiction as a *chronic disease* that can be managed and treated successfully with appropriate care.[32] OUD among pregnant women is no exception and is a serious chronic health condition characterized by needs for long-term treatment and retention efforts. Prescription opioid-related OUD treatment admissions among pregnant women increased in the US from 2% in 1992 to 28% in 2012.[33] In the US, the majority of illicit and medication-related OUD treatment admissions among women in 2012 were for pregnant compared to non-pregnant women.[1] It is unfortunate that approximately 34% of pregnant women who enroll do not complete OUD treatment, with the majority leaving against medical advice (58%), being terminated early by the facility (20%), being incarcerated (5%), or dying (1%).[33]

Rates of relapse for mothers with OUD (in and outside of treatment) in the postpartum period who have achieved abstinence during pregnancy period have been noted to be as high as 80%.[34,35] Such relapse events following periods of abstinence are *potentially fatal* if individuals with decreased tolerance to opioids re-engage in opioid consumption with pre-abstinence quantities.[36-38]

Altogether, OUD is a serious *chronic health condition*, and pregnant women with OUD are at high risk for a number of comorbid medical, behavioral, and psychosocial problems that require concerted efforts—including linking and helping to retain women in OUD treatment as well as to other needed psychosocial resources and care. Fortunately, pregnancy has been observed to be an optimal time for behavior change among women.[39-46]

Following the Chronic Care Model,[47] the most effective models of care for chronic health conditions are designed to proactively engage patients, support clinical decisions based in evidence, employ information systems to guide practice, and promote patient self-management and uptake of community resources. [47-51] Models of care deployed in systems tooled to care for chronic health conditions have been demonstrated to significantly and clinically improve quality of care and patient outcomes.[48-51] For pregnant women with OUD, some components of chronic condition models have been developed and tested. Yet, they have largely been developed and implemented in a fragmented fashion, resulting in limited outcomes. These components of care fall into two general areas: pharmacological and integrated/comprehensive care.

Pharmacological treatment is successful but addresses only one aspect of the chronic condition. The dominant method of care for pregnant women with OUD is medication assisted treatment (MAT), specifically methadone and buprenorphine treatment.[52] *Opioid detoxification is not recommended during pregnancy* given negative impacts on neonate birthweight and possible maternal withdrawal.[53] Managing opioid withdrawal symptomology is significant for pregnant women in order to prevent subsequent opioid relapse. Preventing relapse is summarily important due to the serious health risks associated with illicit opioid use, such as infectious diseases transmission (HIV/HCV) and overdose.[5,54] MAT is key in the care of pregnant women with OUD, but it must also be combined with additional behavioral health services that target psychosocial aspects of addiction.[55,56] However, methadone and buprenorphine treatment studies *rarely* report improvements for outcomes such as engagement in mental healthcare, self-management, or social service resources. Superior models of care for opioid dependent pregnant women, therefore, ideally should be established upon principles of chronic disease management.[57] *It is important note that we recognize both methadone and buprenorphine therapies, as most medications, have strengths and limitations.[52,58] The focus of this study will be to help patients engage in either form of MAT, following the woman's preference, given benefits for mother and infant.*

Integrated and comprehensive care models are valuable but have limitations. To address the multiple and complex issues confronting pregnant women with OUD, integrated and comprehensive care models have been developed, tested, and have moved the field closer towards chronic condition management. *Integrated care models* for pregnant women with OUD are predominantly comprised of multidisciplinary teams providing care[16,59] or outpatient SUD services delivered within hospitals/clinics where pregnant women receive healthcare services[60-62] (i.e., co-located behavioral health models). Results of these models have yielded health improvements for infants born to pregnant women with OUD.[60-62] However, these models exclude important needs of pregnant women with OUD; such as mental health services, housing, food security, and poly-substance use. These models also lack methods for providers to promote self-management and use of resources critical to mothers' health and infant psychosocial development.

Given these limitations, *comprehensive care models* have been utilized among drug dependent women to provide a more complete spectrum of services in one location; including supported housing, counseling, pharmacotherapy, case management, physical/mental healthcare, and child and pediatric care.[58,63-74] Comprehensive care models have demonstrated valuable results, especially for improved maternal and birth outcomes.[64,72] These models have likewise shown less need for child protective services involvement, fewer child removals,[69] and cost-effectiveness. [72] However, most comprehensive care models delivered to pregnant women with OUD report few outcomes for services such as mental health, housing, and food security issues. A larger and more problematic limitation is these models require large amounts of space for in/outpatient services and high volumes of patients/revenue to support staffing expenditures. [71,72] Altogether, currently available integrated care models are limited for effective management of care for chronic disorders, such as addiction, which has serious and harmful consequences. Current comprehensive care models are arguably not easily implemented, scalable, or sustainable. We propose to build on these models to show our *patient navigation (PN)* intervention has the potential to substantially amplify outcomes for both mother and infant, including the breadth of outcomes for both populations in a likely scalable and sustainable model.

Patient navigation for chronic health conditions. A highly promising option for chronic care management for linking and retaining pregnant women with OUD in treatment is the PN model. PN was first developed and implemented in 1990 by Dr. Harold Freeman.[75] As a surgical oncologist, Freeman observed an unsettling 5-year survival rate of only 39% among low income and uninsured women presenting to the Harlem Hospital Center with later stages of breast cancer.[75,76] Freeman initiated affordable breast screenings and the Hospital center began utilizing *patient navigators*. These low-cost services produced substantial improvements for early diagnosis and increased 5-year survival to 70%.[75] Based on this success, PN has been tested and utilized for nearly 25 years for women with breast cancer.[77] PN has evolved to address other conditions; such as HIV, palliative care, spinal disorders, behavioral/mental health disorders, and chronic diseases.[75,78,79]

PN is distinct from other models such as *care coordination* or *basic case management*. The Agency for Healthcare Research and Quality distinguishes these models according to the core aims of each intervention.[78] For example, care coordination is defined by different providers involved in the care of a patient.[78] Each provider is dependent on the others to carry out their role.[78] Case management is defined by the Case Management Society of America's as, "...*a collaborative process of assessment, planning, facilitation and advocacy for options and services to meet an individuals' health needs through communication and available resources to promote quality cost-effective outcomes*." [78,80] PN is unique insofar as its focus is on reducing barriers and guiding patients through complex fragmented healthcare and social service systems.[75,78] PN does not require a floor within a hospital to be allocated for in/outpatient services or require a substance abuse treatment program to be embedded within a healthcare setting. Importantly, PN is a model of care having a patient-centered philosophy that can be provided by *non-professional (bachelors-level)* staff.

Two themes unite and permeate PN models. First, PN breaks down barriers that prevent patients, typically the underserved, from accessing health, psychiatric, social, and family services.[75,76,78,79,81,82] Barriers often include psychosocial issues such as fear/anxiety, communication, transportation, finances, the medical system, and lack of information.[75,76,81] Second, to understand the patient and address their barriers to care, patient navigators develop 1-to-1 relationships to provide personalized support focusing on individual needs.[75,76,78,81] *Despite evidence of its strong effectiveness and support for dissemination, PN has only recently begun to be researched in relation to behavioral health problems*.[83-86] Lasser et al. showed that PN recipients made smoking cessation plans and engaged in treatment more than controls. Bradford et al.[87] found PN recipients with HIV exhibited improved health results, enhanced HIV outcomes,

better physical and mental health, and more health insurance enrollment. Detailed within the preliminary studies section below, our team recently completed a proof-of-concept study where we tested feasibility as well as monitored the initial impact of a PN intervention for pregnant women with OUD receiving MAT in a prenatal care clinic (N=21). [31] Our findings included demonstrating clear intervention feasibility and promising initial results for women in a number of behavioral and physical health domains, including improvements for opioid/substance use, mental health, and prenatal care outcomes. [31]

2.0 OBJECTIVES

2.1 Primary Objectives

Strong evidence supports PN as an evidence-based practice to address various health conditions among different populations and settings.[79,81,85,88,89] Navigation's strengths for populations with OUD encompass individual-level support, case coordination, and strength-based case management that include activities such as: (1) linking patients to OUD treatment, health care, and social services, (2) monitoring and encouraging adherence to treatment, (3) shepherding follow-through with commitments, and (4) ensuring treatment retention and outreach for women who disengage in care. Therefore, given poor neonatal outcomes; [4-7] complex physical, mental, and behavioral health comorbidities, [10-17] and social/legal problems for pregnant women with OUD,[16,29,30] PN is a likely potent model of care that has excellent prospects for improving health and psychosocial outcomes. Accordingly, our *Optimizing Pregnancy and Treatment Interventions for Moms 2.0 (OPTI-Mom 2.0)* project will expand our proof-of-concept project and conduct a small-scale multisite randomized clinical trial. Specifically, this project will achieve three Specific Aims (Table 1). Accomplishing the following Aims establishes critical foundational data for a subsequent fully-powered multisite randomized trial.

Table 1. OPTI-Mom 2.0 Specific Aims:

- To enhance the PN intervention to prevent postnatal relapse
- To expand protocols/procedures for multisite, randomized, health system-wide testing
- To demonstrate the preliminary benefit of PN for facilitating: linkage to treatment/retention in behavioral/physical health care and psychosocial services

3.0 STUDY DESIGN

3.1 Overview of Study Design

Opioid dependent pregnant women who present at Magee-Womens Hospital of UPMC and the University of Utah Hospital ≤32 weeks of gestation will be approached for potential participation in our OPTI-Mom 2.0 study. Our prenatal intervention is designed to span between 8 and 14 weeks and is dependent on gestational age at the time of enrollment. This allows study participants to receive the maximum amount of intervention sessions available prior to delivery. The following Approach Section describes preliminary data we have collected to support this proposal, project design, inclusion/exclusion criteria for participation, recruitment, intervention conditions, data collection/analysis, and timeline.

3.2 Duration of Study and Visit Schedule

This study will require 36 months to complete. Patient recruitment will last 15 months, intervention deliver will last 24 months, and assessments will last 30 months. As indicated, the prenatal portion of the study will include up to 10 sessions that span between 8 and 14 weeks. In addition, we will also provide 4 postnatal interventions that span 8 weeks. Each of these sessions lasts 1-1.5 hours. All participants, in the treatment or control group, will be required to complete 4 standardized assessments, which will occur at baseline, following the completion of the prenatal portion of the intervention, following the postnatal portion of the intervention at approximately 2 months post delivery, and 6 months following delivery. See SOP for data collection.

4.0 OUTCOME MEASURES

4.1 Primary Outcome Measure

The primary outcomes in this study are (1) OUD and other SUD treatment linkage/retention, (2) opioid abstinence, (3) adherence to MAT, and (4) linkage/retention in psychosocial services.

4.2 Secondary Outcome Measure(s)

Secondary outcomes of this study involve capturing prenatal care, HIV/HCV risk behaviors, depression and anxiety, and child/mother indicators.

4.3 Study Timeline

Quarter 1 of the project will involve IRB application/completion, intervention augmentation/adaptation, protocol adaptation/expansion, and assessment battery completion. The first 2 quarters will also involve hiring/training personnel. Subsequently, patient recruitment will occur over 15 months, with intervention delivery and outcome assessments happening simultaneously. Intervention delivery and outcome assessments will extend 9 and 15 months beyond recruitment, respectively, in order to allow sufficient time to complete each. DSMB meetings will also happen semi-annually.

5.0 STUDY POPULATION

This study will recruit adult women who are pregnant, with opioid use disorder, who are presenting at the Magee-Womens Hospital of UPMC or the University of Utah Health system for any care needs.

5.1 Participant Inclusion Criteria

This study will recruit women for participation meeting the following inclusion criteria:

- Adult (≥18 years)
- English speaking
- Pregnant women (pregnancy status verified by gestational age >6 weeks from last menstrual period confirmed by ultrasound)
- OUD verified by examination of medical records for an OUD diagnosis and the DSM Checklist (modified from the DSM-IV to confirm current diagnosis for substance use disorders)
- Plan to carry their babies to delivery verified by patient self report

5.2 Participant Exclusion Criteria

All women meeting any of the exclusion criteria at baseline will be excluded from study participation:

- Experienced a psychotic or a manic episode in the last 30 days documented in their medical record or self report
- Beyond the 32nd week of gestation
- Cannot provide collateral contact information of 2 persons
- Cannot provide a reliable phone number
- Plan to move from the area within study recruitment to 6 months after their delivery
- Inability or unwillingness of subject to give written informed consent.
- Other factors that would cause harm or increased risk to the participant or close contacts, or preclude the participant's full adherence with or completion of the study
- Has been on buprenorphine or methadone for >6 weeks.

5.3 Strategies for Recruitment and Retention

Two hospitals will be utilized as locations for identifying, recruiting, and engaging with potential project participants. The following methods will be used to recruit women into this study.

- Behavioral health staff at both performance sites will be trained in referring possible patients to our study. Behavioral health staff will be trained in the inclusion and exclusion criteria for this study. OPTI-Mom research staff will reach out to hospital staff each month to ensure they are familiar with study and encourage them to referral patients. When they encounter patients who they believe will be eligible for this study, they will relay to patients that they might be eligible for study participation (see Study Information Form). If the participant expresses interest in learning more about the study opportunity, the behavioral health staff member will facilitate contact with the study staff either by directly connecting the patient to the staff in person or via phone. If time does not allow for directly connecting the patient to the study staff, the patient will be provided with a study advertisement

handout and/or the behavioral health staff person will relay patient contact information to the study staff.

- Patients will be contacted through the University of Pittsburgh Pitt+Me research registry. Patients with ICD9/10 codes for pregnancy and OUD or opioid overdose will be identified in this registry. Potential participants in the Pitt+Me system have already acknowledged interest possibly participating in research. All participants are UPMC patients. Once contacted by Pitt+Me, these patients contact study staff who will screen for possible inclusion in the study.
- Study staff at both performance sites will also be trained to identify potentially eligible patients using patient medical records systems to locate women with OUD and who are pregnant (See Magee EMR review 1-2 and Utah EMR review). Once identified in the medical record systems, patients will be mailed a letter informing them they are eligible for a research study. Letters will be mailed to participants as much as weekly. Letters will not disclose how patients are possibly eligible in order to protect privacy. Patients will be invited to contact study stuff to learn more about the study. Patients will also be informed in the letter that research staff will contact them after a week of not hearing back from them. After a week, research staff will reach out to potential patients.
- Study flyers will also be posted within the hospitals and clinics bulletin boards, waiting rooms of the performance sites and local outreach sites and facilities (see Advertisement). These flyers will contain general study information and study staff contact information.

Study staff who contact patients will do so from the University of Utah SUPeRAD clinic, staff research office space in Research park, staff office space from Magee Womens Research Institute or an appropriate and private location. Calls will be made from study use only cell phones or from office phones. Voicemail and other messaging is all password protected. If patients provide an email address, study staff may also contact them via this method. All computers and university related email accounts used to contact potential participants will be password protected.

Both sites will capture the number of eligible patients approached, number of patients approached, number of patients who chose to screen and those who did not. Reason for not screening will be captured. We will also capture the reason for why patients who were screened as ineligible were not eligible. Finally, we also capture the number of patients who chose to provide informed consent and those that did not. We will likewise capture the reasons patients may given for not providing informed consent and enrolling in the project. All these records will be captured using REDCap.

In order to ensure adequate follow up with participants; contact and locator information will be used to engage patients through multiple mediums, including phone, text, email, social media, and mail. See SOP for Continued Engagement.

6.0 SITES

6.1 Number of Sites and Participant Flow

Two sites will be used for participant recruitment in this study. A total of 122 women will be recruited for participation in this study. We anticipate an even distribution of 61 women recruited at each site. For the 61 women recruited and randomized to the PN condition, we expect approximately 30 will be recruited at the University of Utah and 31 at the University of Pittsburgh. Based on estimates of a recruitment window of 15 months and active intervention delivery across 24 months, we will recruit approximately 5 patients per month between both sites. In terms of monthly patient caseload during the 6 busiest months of the study, each site will have approximately 9 to 12 active (pre and postnatal) participants at one time.

7.0 STUDY PROCEDURES

7.1 Screening Visit

Once patients have been identified and have expressed interest in learning more about this possible study opportunity, staff will receive permission to screen these patients using the inclusion and exclusion criteria. Permission for screening will be obtained using an oral screening consent form (see SOP for Screening, Consent, Locator, Initiation, Assessment and Blinding). Those who screen positive will then be provided with the full consent documents for study enrollment.

7.1.1 Informed Consent Procedures for Participants

Study procedures and the potential risks and benefits of participating in the trial will be explained to participants (see SOP for Screening, Consent, Locator, Initiation, Assessment and Blinding). We also will obtain permission to audio record intervention sessions for intervention fidelity monitoring purposes. Given the multi-site nature of the trial, it is possible that ancillary studies will be proposed before or after the study begins recruitment. For this reason, during the informed consent process, we also will seek permission to contact the participant in the future about other study opportunities. Staff will be available to answer questions about the consent form while participants are reviewing it. Prior to signing the consent form, the participant must pass a brief consent comprehension tool to illustrate comprehension of the study activities. After successful completion of the tool and signing the consent form, participants will be given a copy to keep for their records. The informed consent process will take approximately 20 minutes to complete.

Participants who pass the screen and consent will complete a locator information form which will be used to contact them to remind them of follow-up visits and to locate participants who cannot be found. Trained study staff members will work with the participant to complete this form. When completing this form, participants will be required to provide their names, addresses, and telephone numbers as well as contact information for at least 2 other persons. Locator information will be updated at the follow-up visits and at any other time during the study, as needed. The locator information form will take approximately 5-10 minutes to complete. Patients not able to provide at least 2 collateral contacts will not be allowed to participate in the study. Participants will be directed to inform their 2 collateral contacts that they are in the study. The participant will also be informed that she may disclose any level of detail about her involvement with the study to her locator contact she wishes. By sharing this information, should the study contact the collateral, these individuals will know the participant is already in the study. Locator information will be reverified at each follow up visit.

7.2 HIPAA Authorization and Medical Record Release Forms

As part of the enrollment process, we will obtain written permission from the patient to access their University of Utah and University of Pittsburgh medical records. We will likewise obtain permission from participants to access services records from community agencies where they may obtain health and social services.

7.3 Baseline Visit

After patients complete the locator information form, they will complete a baseline assessment. The study staff member administering the assessment will have completed all required CITI training modules. Drs. Cochran and Krans will also train the study staff in survey administration methods, specifically with how to appropriately ask sensitive questions and to respond to responses from patients regarding sensitive topics (including reporting information to study PIs

by the participant regarding intention to harm self or others). Training will include Drs. Cochran and Krans going over the survey with the research assistant, modeling appropriate administration, practicing administration, and supervised administration for the first 3 subjects enrolled in the study. The study baseline assessment will happen at the SUPeRAD clinic, research offices, Magee Womens Research Institute, or other appropriate and private locations. Assessments will be completed using REDCap surveying technology. Survey responses will be reviewed by study staff to ensure completeness. Completed surveys will be immediately saved online. The baseline assessment will take approximately 30-45 minutes.

7.4 Randomization

Following the baseline assessment, participants will be randomized on a 1:1 basis to PN or standard care (i.e., short-term case management + referral). The study statistician will create a randomization list to assign patients to treatment or control conditions. The statistician will also review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new patient due to the intent-to-treat nature of the study.

7.5 Treatment/Intervention

Standard care. The standard care condition at Magee and the University of Utah hospitals includes brief case management and referral. The brief case management involves the participant speaking to a hospital social worker who conducts a patient needs assessment in the areas of behavioral health and social services. All patients will be referred to MAT and any identified behavioral health or social service needs. For MAT, Magee-Womens Hospital offers resources for onsite induction to methadone or buprenorphine (mono-product), with continued methadone maintenance only provided by community partners and continued buprenorphine offered by an internal Magee clinic or community partners. University of Utah patients are offered buprenorphine induction and maintenance (buprenorphine-naloxone product) at a local University of Utah outpatient clinic or from community partners. Methadone services for University of Utah patients are only provided by community partners. Staff social workers at Magee and the University of Utah will be provided with information on the study each quarter during the study recruitment phase and be instructed to closely follow and not deviate from their hospital standard care protocol. These quarterly meetings/trainings will be delivered in order to prevent threats to internal validity and biasing study outcomes.

Patient navigation (PN). Details of the navigation can be found in the PN Intervention Manual. The PN intervention will be delivered by the study navigator. Table 4 contains details of the PN intervention. The PN intervention will initiate following participant recruitment. *It is important to note that in Table 2, PN sessions do not strictly coincide with specific weeks of pregnancy since the women can be recruited up to ≤32 weeks of gestation*. The *prenatal portion* of the intervention includes up to 10 sessions delivered prior to delivery. The *postnatal portion* of the intervention will be delivered as 4 sessions over 8 weeks. Women who complete the intervention before delivery will receive regular calls/texts until delivery wherein the navigator will encourage and reinforce abstinence and treatment retention (see SOP for continued engagement). All contact will be reported by staff in a participant contact log developed for the study that will be used to quantify level of patient contact.

Our PN model is based on the work of Parker[37] and the recently completed Project HOPE study (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users).[38,110] The study navigators will receive a two day training in motivational interviewing tailored to the study intervention manual and must demonstrate motivational interviewing proficiency assessed by trainers. The navigators will also receive a one-day training in the intervention protocol by study

investigators. Navigators will complete 3-5 practice sessions, which will be audio recorded and assessed using intervention checklists. Feedback from practice sessions will be shared with navigators in directly and in group discussions. Intervention fidelity checking will also occur throughout the study with navigators audio recording all PN sessions, which will be selected at random for fidelity assessments and feedback by the study coordinator and project investigators.

The primary goal of the current PN intervention is linking patients before and after delivery to treatment/psychosocial care and clinical support for participants' retention in those services. All PN patients will be referred to MAT by the study navigator (see standard care description above for site differences for MAT resources). *It is through the navigator linking and helping to retain participants to OUD, other SUD, medical, mental health, social, and family services that will stimulate positive short- and long-term outcomes for mother and infant*. While Magee and the University of Utah hospitals facilitate initiation into MAT, a major challenge for women is linking to services for ongoing MAT and subsequently being retained in care. Patients will be encouraged to work with their providers to choose the form of medication, buprenorphine or methadone, which will best meet their needs. The navigator will support and encourage the patient to follow through with this treatment. The PN intervention will also target better compliance with pre/postnatal maternal healthcare, more effective transition of newborns into pediatric care, and relapse prevention (i.e., Aim 2). The PN intervention specifically encompasses two complementary and necessary services: strengths-based case management (SBCM) and 1-to-1 clinical support (see Table 2). PN sessions will last 1-1.5 hours. Furthermore, given the challenges keeping this population engaged in care, the intervention emphasizes community outreach. For example, the navigator can visit the neighborhoods to meet participants' social and family networks to empathically encourage and support engagement with health, social services systems, and recovery support (i.e., narcotics anonymous, alcoholics anonymous) if patients become disengaged in care or follow up.

SBCM is an evidenced-based component of the PN model that has been demonstrated to help individuals with substance use disorders and chronic health conditions engage in needed care.[34,35] The navigator will apply the specialized skills of SBCM to link patients to ongoing MAT services and guide participants to active engagement in health and social services. SBCM gives patients responsibility for, and ownership of, their recovery.[35] SBCM has been shown to have a variety of positive effects, particularly treatment retention[111,112] and linkage with community services.[113] SBCM utilizes patients' strengths for goal setting and developing a working alliance[35] between providers and patients. The specific elements the navigator will focus on include: helping patients obtain and complete paperwork; accessing and engaging in drug/mental health counseling/treatment/mutual support, social services uptake, MAT linkage/retention, and engagement in pre/post-natal care and pediatric/developmental care for newborns. It is important to note that participants and the navigator will collaborate to identify *already existing health and community services* that participants will subsequently engage in with the navigator's assistance.

One-to-one clinical support is a paramount PN component for identifying, establishing, and retaining health behavior improvement goals. One-to-one clinical support is designed to motivate and assist patients recognize and overcome internal/external barriers to care, including: emotional support, decision support, lifestyle change support, monitoring outcomes of screening/diagnostics, health behavior, and HIV/HCV prevention education.[37] HIV/HCV prevention messaging will address needle sharing and unsafe sex. Patients will receive support and verbal reinforcement for completion of paperwork, engaging in drug/mental health treatment, social services uptake, agonist adherence, and engaging in pediatric/developmental care for their infants. One-to-one clinical support will be delivered using *motivational interviewing skills*.[114] Motivational interviewing is an evidence-based approach for promoting health behavior change in healthcare settings.[114,115] The navigator will collaborate with participants to resolve ambivalence toward change by guiding them to establish their own goals

and strategies, giving them ownership in outcomes, helping build self-efficacy, and increasing the likelihood of achieving abstinence and MAT retention goals. We have also aligned PN session objectives to support and assist women to prepare for, discuss, and successfully complete specific maternal milestones.

7.6 Premature Withdrawal of Participants

All participants will be followed for the duration of the study unless they withdraw consent, are no longer pregnant due to spontaneous abortion (miscarriage) or termination that was unplanned at the time of enrollment, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, DSMB early termination of the study for safety or effectiveness determination.

7.7 Study Halting Rules

The study will be halted based on lack of funding.

7.8 Follow-Up

Participants will be assessed at baseline, following the completion of the prenatal portion of the intervention, following the postnatal portion of the intervention at approximately 2 months post delivery, and 6 months following delivery. See SOP for data collection. Appointments for follow up sessions will be made with participants by study staff. At the follow up visits, the first step in the assessment will be to confirm participant contact information and to ensure locator information has not changed. Following contact information verification, patients complete a survey assessment similar that completed at the baseline assessment. The study follow up assessments will happen at the SUPeRAD clinic, research offices, Magee Womens Research Institute, or other appropriate and private locations using REDCap surveying technology. Survey responses will be reviewed by study staff to ensure completeness. Completed surveys will be immediately saved online. The follow up assessments assessment will take approximately 30-45 minutes at each visit—see urine drug screen SOP.

7.9 Blinding

7.9.1 Type of Blinding

This study is a single blinded randomized clinical trial.

7.9.2 Maintenance of the Blind

The individuals blinded to the study condition will be those conducting the study assessments. The baseline assessment will be blinded given that the randomization will not be revealed until after the assessment is completed. The follow up assessments will be conducted by a blinded research assistant.

7.9.3 Breaking the Blind

As the research assistant is the only blinded party, there is no scenario in which the blind will need to be broken. Investigators providing clinical management and decision-making are informed of each participants randomization result.

7.10 Participant Reimbursement

Women will receive $30 for enrolling in the study and completing the baseline assessment, $40 for completion of the second assessment, $50 for the third assessment, and $75 for the final assessment. Patients that complete all 4 assessments will be given a completion bonus of $50. Patients will also be provided with a $10 compensation for each navigator session they attend to cover costs associated with transportation and/or parking. Participant compensation administration will be carried out by the study project coordinator or research assistants.

8.0 STUDY ASSESSMENTS

A full and complete list of all assessments used in the study is to be included in the following sections.

Outcome	Domain	Name	Source	Screen	Base	PreNat	2mo	6mo
1/2ary	Engage	Treatment Services Review	Self-Report		x	x	x	x
1/2ary	SUD	Timeline Follow Back	Self-Report		x	x	x	x
1ary	Engage	Substance use treatment visits	Medical record		x	x	x	x
1ary	Engage	Psychiatric care visits	Medical record		x	x	x	x
1ary	SUD	Urine toxicology	NA	x	x	x	x	x
1ary	Engage	Social service visits	Agency record		x	x	x	x
2ary	HIV/HCV risk	Risk Behavior Assessment	Self-Report		x	x	x	x
2ary	Social	Maternal Social Support Index	Self-Report		x	x	x	x
2ary	Social	Parenting Stress Index-Short Form	Self-Report		x	x	x	x
2ary	Social	Maternal Attachment Inventory	Self-Report		x	x	x	x
2ary	Engage	Adequacy of Prenatal Care Utilization	Medical record				x	
2ary	Engage	Pre/post maternal care visits	Medical record		x	x	x	x
2ary	Engage	Pediatric visits	Medical record		x	x	x	x
2ary	SUD	Neonatal abstinence syndrome	Medical record				x	
2ary	Engage	Pre/post maternal care visits	Medical record		x	x	x	x
2ary	Engage	Pediatric visits	Medical record				x	x
Covar	SUD	Drug Abuse Severity Test 10	Self-Report		x	x	x	x
Covar	SUD	Alcohol Use Disorder	Self-Report		x	x	x	x

		Identification Test						
Covar	SUD	Fagerstrom Test for Nicotine Dependence	Self-Report		x	x	x	x
Covar	Health	Short Form 36	Self-Report		x	x	x	x
Covar	Psych	Patient Health Questionnaire	Self-Report		x	x	x	x
Covar	Social	Addiction Severity Index (employment)	Self-Report		x	x	x	x
Covar	SUD	DSM 5 Checklist	Self-Report	x	x	x	x	x

8.1 General Measures

8.1.1 Inclusion/Exclusion

This form lists each inclusion and exclusion criterion to document eligibility. Eligibility is assessed continually as appropriate. Only participants who continue to meet study eligibility criteria are allowed to continue with the screening process, consent and randomization.

8.1.2 Locator Form

A locator form is used to obtain information to assist in finding participants during treatment and at follow-up. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected, as well as additional participant information such as social security number and other information to aid in searches of public records. This information will be collected at screening and will be updated at each visit. No information from this form is used in data analyses.

8.1.3 Demographics Form

The Demographics form collects information about demographic characteristics of the participant, including date of birth, ethnicity, race, education, employment status, and marital status. This form is completed at screening.

8.1.4 Study Completion Form

This form tracks the participant's status in the study. It is completed at the final postnatal visit or once the 6-month follow-up visit window lapses for participants who do not complete this final follow-up. This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the site PI attestation of review of all study data.

8.2 Clinical and Safety Assessments

8.2.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

At each visit the study navigator assesses for AEs and SAEs by asking the study participant, “How have you been feeling since your last visit?” AEs and SAEs may also be spontaneously reported to study staff at any visit following consent. AEs and SAEs suggesting medical or psychiatric deterioration will be brought to the attention of a study clinician for further evaluation and management. Visits will emphasize overdose risk and risk-management. Any reported overdose is recorded as an AE or SAE, or in a separate form. AE and SAE reporting is according to the reporting definitions and procedures outlined in the protocol and in accordance with applicable regulatory requirements.

For the purpose of this study, the following AEs do not require reporting in the data system but is captured in the source documentation as medically indicated:

Grade 1 (mild) unrelated adverse events. This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the study intervention.

8.2.2 Suicidal Behavior Evaluation

Within the Patient Health Questionnaire is embedded a validated single item suicide screening tool. This item is assessed at each visit. If the participant screens positive for depression, the navigator will ensure the participant contacts the Resolve Crisis Center to arrange for follow up (1-888-796-8226) within the University of Pittsburgh or the Crisis and Interventional and Hospital Diversion Crisis Line within the University of Utah (1-801-587-3000). If the participant screens positive for suicidality, the navigator will immediately follow the study Suicide Management Plan (see REDCap form). Similarly, if the participant appears to be intoxicated or reports experiencing symptoms of opioid withdrawal, the navigator will immediately notify the site study physician who can further assess and direct steps for possible additional care depending on participant need.

9.0 TRAINING REQUIREMENTS

9.1 Overall

A Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training.

Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, medication management for pharmacological studies, study interventions, safety and safety event reporting, study visits and procedures, data management, quality assurance, laboratory procedures, etc. The University of Utah site is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The University of Utah site also is responsible for training related to data management, the electronic data capture system, and good data management practices.

Study staff is required to complete institutionally required training per their research site, Institutional Review Board(s), and authorities with regulatory oversight. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site Principal Investigator and the project coordinator. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

10.0 STATISTICAL DESIGN AND ANALYSES

10.1 General Design

This study design for this project is a small scale, multisite, phase 2, single blinded, randomized clinical trial. Randomization will be stratified by hospital site and performed in blocks of 6 to ensure an even distribution of Magee and University of Utah participants in PN and standard care groups.

10.1.1 Study Hypotheses

H1: PN recipients will have superior linkage and retention in: (a) OUD and other SUD treatment, (b) psychosocial services, and (c) pre/postnatal care compared to standard care.

H2: A larger portion of PN patients will be (a) MAT adherent and (b) drug abstinent compared to standard care.

H3: Higher levels of engagement/retention in care will positively moderate improvements in: (a) abstinence, (b) HIV/HCV risk behaviors, (c) depression/anxiety, and (d) child/mother outcomes (e.g., health care, NAS, stress).

10.2 Rationale for Sample Size and Statistical Power

10.2.1 Projected Number of Sites

Two hospitals will be utilized as locations for identifying, recruiting, and engaging with potential project participants. Both hospital locations are major centers of activities for women's health within their respective health care systems. Both study hospitals are destination service centers for pregnant women to receive testing, care, and for eventual delivery. Specifically, Magee-Womens Hospital of UMPC is a hub for women's health care in Allegheny County as well as western PA. This hospital provides a number of health care services to pregnant women, including emergency department, obstetrics/gynecology, midwifery, and fertility services. The University of Utah is likewise a hub for care in Salt Lake City and the state of UT. This hospital is an urban level-1 trauma center with a number of services available for pregnant women, which include obstetrics/gynecology, midwifery, and fertility services.

10.2.2 Projected Number of Participants per Site

Given this study is designed as a pilot study testing an expanded intervention and protocols/procedures, sample size is not based on a power estimate. Rather, our sample size is based on our estimates of how many patients can be screened and consented within the study timeframe, an appropriate method for pilot studies.[90] Based on the above detailed counts of MAT inductions among pregnant women from Magee-Womens Hospital from 2013 and 2017, we anticipate an average of 141 potential women recruits each year. Further, based on the above described numbers of total pregnant women with OUD/overdose (i.e., poisoning) from the University of Utah from 2015-2017, we anticipate an average of 58 potential recruits each year. Therefore, if we screen and recruit patients across 15 months, and if 70% are eligible and interested, and of those, 70% provide informed consent; we will recruit a total of 122 patients in this study who will be randomized to the PN (n=61) or standard care conditions (n=61). ***Importantly***, working to recruit, randomize, provide PN/standard care, and retain 122 pregnant women with OUD during the study timeframe will allow us sufficient time to learn to implement and manage this study across 2 sites in preparation for a subsequent fully-powered trial.

While definitive estimation and hypothesis testing are not the aim of this pilot study, the target sample sizes will allow estimation of odds ratios via 95% confidence intervals comparing outcome rates in the treatment and control arms, while accounting for within site clustering, with lower bounds differing from the odds ratio estimate by a factor of 1/3 to 1/2 and upper bounds differing from the odds ratio estimate by a factor of 2 to 3 for a broad range of overall rates, true odds ratios, and magnitude of site-to-site effects. In particular, the pilot study will allow detection of strong signals of preliminary benefit, and provide suggestions of benefit for more subtle signals.

Of the 122 women recruited to participate in this project, based on our preliminary information about patient flow at each site, we expect that 61 will be recruited at each site. For the 61 women recruited and randomized to the PN condition, we expect an equal recruitment distribution at each site. Based on estimates of a recruitment window of 15 months and active intervention delivery across 24 months, we will recruit approximately 5 participants between both sites. In terms of monthly caseload during the 6 busiest months of the study, each site will have approximately 9 to 12 active (pre and postnatal) participants at one time.

DSMB recommendation on November 1, 2019 was to evenly distribute recruitment goals for both sites. This is due to more outside agencies in Pennsylvania that are offering prenatal care and services for women with substance use disorders.

10.3 Statistical Methods for Primary and Secondary Outcomes

We will employ descriptive statistics to calculate measures of central tendency, frequencies, and proportions for patient demographics and substance use, health, social, and mother/child indicators. T-tests and χ^2 tests will be used to assess mean and proportion differences between outcome variables by study group at each time point. Specifically, we will examine unadjusted differences between PN and standard care patients for linkage/retention in: (a) OUD and other SUD counseling, (b) psychosocial services, and (c) pre/postnatal care compared to standard care. We will also examine unadjusted differences between groups for MAT adherence, opioid and non-opioid drug abstinence, HIV/HCV risk behaviors, depression/anxiety, and child/mother outcomes (e.g., NAS, parental stress, attachment, and maternal social support).

We will also develop a series of multilevel models to examine treatment, time, and covariate effects associated with our primary and secondary study outcomes (Equation 1[91,92]). The multilevel framework allows for a flexible treatment of time where change as a putative outcome may be nonlinear, accelerates, or decelerates at different rates across time. The framework is also forgiving of unequal numbers of observations and unequal spacing of observations across participants (i.e., missing data patterns). Models will be constructed using a model-building sequence proposed by Singer and Willett,[93] in which: (a) empirical growth plots will be examined visually, (b) an unconditional model will be fit, (c) an unconditional linear growth model will be fit, (d) unconditional non-linear models (e.g., a piecewise model) will be fit, (e) the models' fit in the prior steps will be compared using the Akaike Information Criterion to determine the best growth model, and (f) time-invariant (e.g., baseline mental health diagnoses) and time-varying (e.g., drug use) predictors will be added to the models. We will examine the association of these predictors with the study outcomes across time. We will also test higher levels of service linkage/retention as moderators for improvements in (a) abstinence, (b) HIV/HCV risk behaviors, (c) depression/anxiety, and (d) child/mother outcomes.

Included below is the equation for a random-coefficient multilevel growth model. The Y in the equation represents a binary opioid abstinence outcome, for example, for the i th participants at time *t.* The symbol "~" indicates that the binary response with linear predictor given by the right hand side in the context of a logistic mixed effects model, with random effects for site, and potentially time within site. The primary variable types are represented in the equation: (a) *time* is

a variable representing time that may require multiple time variables in the event of nonlinear change (e.g. quadratic), (b) *time-varying* is any variable measured at each time point, and (c) *invariant* is a variable measured at the person-level. The model below can easily be extended to a third level if it is determined that there is variability in coefficients across centers.

	Level 1:	$Y_{ti} \sim \beta_{0i} + \beta_{1i}time_{ti} + \beta_{2i}time\text{-}varying_{ti} + \beta_{3i}time_{ti}time\text{-}varying_{ti}$
Equation 1.	Level 2:	$\beta_{0i} = \gamma_{00} + \gamma_{01}invariant_i + u_{0i}$
		$\beta_{1i} = \gamma_{10} + \gamma_{11}invariant_i + u_{1i}$

11.0 REGULATORY COMPLIANCE, REPORTING and MONITORING

11.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality assurance tool.

11.2 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the Institutional Review Board (IRB) of record in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

11.3 Institutional Review Board Approval

Prior to initiating the study, site investigators will obtain written IRB approval to conduct the study at their respective site. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site, and must be available at any time for audit.

The University of Utah will be the IRB of record for the protocol, and will provide study oversight in accordance with 45 CFR 46. Participating institutions have agreed to rely on the University of Utah and have entered into reliance/authorization agreements for the study protocol.

11.4 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation. The informed consent form will include all of the required elements of informed consent, and may contain additional relevant consent elements. Each study site must have the study informed consent approved by their IRB(s). To confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(a), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(b), a copy of the IRB-approved consent, along with the IRB study approval, must be sent to the University of Utah prior to site initiation and with each subsequent consent revision. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related

procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible for QA review. Every study participant will be given a copy of the signed consent form.

Prior to informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

The study does not preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. It is in conformance with 42 CFR 2.52, which allows for research-related provisions with regard to the disclosure of substance use disorder patient identifying information in the absence of the informed consent process and HIPAA authorization.

On 4/2/2020 the University of Utah IRB, the IRB of record, approved the use of eConsent technology via REDCap in response to the COVID-19 pandemic as a supplement to in-person consent. For each site, the REDCap project includes a downloadable consent, each page of the IRB stamped consent, the consent comprehension tool, the option to authorize or decline audio recording of PN sessions, the option to decline or consent to enrollment prior to electronically sign and dating, and the ability to download a copy of their signed consent. The signed consent is available for review and download by the lead and enrolling site. Research staff delegated to obtain informed consent will continue to follow the procedures outlined above virtually. In person consent is not restricted with this amendment, however, it is dependent on local guidelines and regulations.

11.5 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation, and ensuring that the investigation is conducted in accordance with the protocol. As this study does not have a sponsor assigned monitor, the investigator has

delegated this responsibility to the lead site who will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation review, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations can be reported as a protocol deviation and submitted to the IRB for further review.

11.6 Participant and Data Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. By signing the protocol signature page, the investigator affirms that information furnished to the investigator will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

To further protect the privacy of study participants, the lead investigator will obtain a federal Certificate of Confidentiality (CoC) from NIH, which protects identifiable research information from forced disclosure, and will distribute it to all sites when received. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

Per Section 2012 of the 21st Century Cures Act all ongoing or new research funded by CDC as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically covered by a CoC.

11.6.1 Health Information Portability Accountability Act (HIPAA)

Study sites will be required to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the IRBs or Privacy Boards of record and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

11.7 Investigator Assurances

11.7.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial

interest. Everyone with decision-making responsibilities regarding the protocol will confirm annually that they have met their institutional financial disclosure requirements.

11.8 Clinical Monitoring

Investigators will conduct periodic review to examine whether study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. Reviews will occur at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Reviews will verify that study procedures are properly followed, site personnel are trained and able to conduct the protocol appropriately, whether submitted data are accurate and in agreement with source documentation and review regulatory/essential documents such as correspondence with the IRB. Reports will be prepared following the visit and forwarded to the principal investigator and site principal investigators. Reviewers will have the opportunity and ability to view any study-associated document or file. If the review of study documentation indicates that additional training of site study personnel is needed, the reviewer will undertake or arrange for that training.

11.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

If a participant in the study becomes a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under Subpart C of 45 CFR 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated participant must be suspended immediately. The lone exception to this regulation is if the investigator asserts that it is in the best interests of the prisoner-participant to remain in the study while incarcerated. The investigator must promptly notify the IRB of this occurrence.

11.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

11.11 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to be maintained by the investigators in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The sponsor and Principal Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

11.12 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved consent form and signed participant consent forms. As part of participating in a CDC study, each site will permit authorized representatives from CDC and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

11.13 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Corrective action plans will be reviewed/approved by the PI with overall approval by the IRB of record. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. All protocol deviations will be recorded, reviewed by the PI, and saved in the study electronic files. Additionally, each site is responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

11.13.1 Adverse Events (AEs)

Specific adverse events that will be collected in this study are described in further detail in Appendix A.

Two study clinicians are have been appointed in this project, who will review or provide consultation for each Serious Adverse Event (SAE) as needed at each site. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. Study clinicians will also provide advice for decisions to exclude, refer, or withdraw participants as required.

Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will

be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

12.0 DATA AND SAFETY MONITORING PLAN

1.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events. All adverse events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol, see Appendix. The occurrence of AEs and serious adverse events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable. Reportable AEs are required to be entered into the data system within 7 days of the site staff becoming aware of the event. Reportable SAEs (including death and life-threatening events) are required to be entered into data system within 24 hours of site's knowledge of the event).

B. Medical Monitor

The site study clinician is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported data capture program. The site clinician will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed, the study clinician will discuss the event with the site staff. All AEs are reviewed on a regular basis to observe trends or unusual events.

C. Data and Safety Monitoring

The study Data and Safety Monitoring Plan will involve monthly meetings held to discuss subject health and general research issues. Any serious and unexpected adverse changes in a subject's clinical status that are associated with the research intervention will be immediately brought to the attention of the PI and University of Pittsburgh site PI. A description of any such events will be conveyed to the IRB. Meetings will include, but not be limited to, reviewing the following data for patients:

- Level of depression
- Attendance prenatal care
- Adherance to MAT
- Food/housing insecurity
- Issues with interpersonal violence
- Illicit drug use

The DSMP will also involve the PI, site PI, and coinvestigators evaluating the progress of the research study, including assessments of data quality and timeliness and participant recruitment, accrual, and retention. Clinical outcomes and adverse event data will be used to determine whether there is any change in the anticipated benefit-to-risk ratio for study participants and whether the study should continue as originally designed, should be changed, or should be terminated. The PI, site PI, and coinvestigators will also assess external factors or relevant information (e.g., pertinent scientific literature) that may have an impact on the safety of study participants or the ethics of the research study and review study procedures designed to protect the privacy of the research subjects and confidentiality of their research data.

We will also recruit two Data Safety Monitoring Board members, one from the University of Utah and one from University of Pittsburgh, who will review information generated by the DSMP

semiannually and who can provide safety recommendations to the study team. The DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for DSMB meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs. The DSMB will make recommendations as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment). Following each DSMB meeting, outcomes will communicated, based on DSMB recommendations, in writing to the study PI. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a semi-annual basis. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., pharmacy, research office), source data/documentation, and reports for the purpose of monitoring and auditing, as well as inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and PI supervision and involvement in the trial. The reviewer will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the reviewer following each site visit. These reports will be sent to the site PI and study PI.

E. Database Protection

The database will be secured with password protection. The manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information.

F. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information That Meets Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

AEs and concomitant medications will be assessed and documented at clinic visits. Individuals who experience an AE that compromises safe participation in the study will be discontinued from further intervention and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end visit to assure safety and to document outcomes.

Longterm Data Storage and Sharing

Data for this project be will stored on University of Utah cloud computing servers and/or archives for long term-storage. Electronic access to these data are password protected, encrypted, and HIPAA compliant. Physical access will be protected by storage in locked cabinets inside locked facilities. Data will be de-identified before sharing with other investigators on a need to know basis, and on the agreement that once the data analysis is complete, the data will be returned or destroyed. Data will only be shared with investigators with appropriate data sharing agreements and/or Institutional Review Board for Human subjects approvals, as required.

13.0 DATA MANAGEMENT

13.1 Design and Development

The University of Utah site will be responsible for development of electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating staff at both sites on applicable data management procedures. This will also include the University of Utah site working to: 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning. The remainder of this section provides an overview of the data management plan associated with this protocol.

13.2 Site Responsibilities

The University of Utah will provide study leadership for data management, analysis, and reporting. The University of Utah will train staff at the University of Pittsburgh in data collection requirements, procedures, and security. Both sites will ensure before participant and other study data is uploaded to the data capture program, patient reported responses to interview questions are complete and accurate. Site audits will involve the University of Utah project coordinator reviewing uploaded study data to ensure completeness and accuracy of data. A trained University of Utah research staff member in day to day study operations will perform data reviews to ensure uploaded data from sites are complete and accurate.

13.3 Data Collection

The data collection process consists of direct data entry at the study sites into the data capture program. In the event that the data capture program is not available, the University of Utah site will make available a final set of guided source documents and completion instructions. Data entry into the data capture program should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

13.4 Data Editing

Completed data will be entered into the data capture program. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the data capture program.

13.5 Data Transfer/Lock

The University of Utah study statistician and statistical program will conduct final data quality assurance checks and “lock” the study database from further modification.

13.6 Data Quality Assurance

To address the issue of data entry quality, the University of Utah will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. The management plan will entail the project coordinator generating regular data quality summaries during the course of the protocol. This will specifically involve building composite indicators and running descriptive statistics each month during participant recruitment and follow up.

PROTOCOL SIGNATURE PAGE

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version X of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.

- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.

- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.

- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

14.0 APPENDIX A: ADVERSE EVENT REPORTING AND PROCEDURES

Each participating site's Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events. See AE form in the electronic data capture program.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any unexpected medical occurrence in humans, whether or not considered study intervention related which occurs during the conduct of a clinical trial. Changes from baseline in clinical status; i.e., death, miscarriage, pre-term birth, overdose, relapse, child protective services involvement including child removal; that are considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study intervention caused the event.

Adverse reaction is any adverse event caused by the study intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study intervention, must be reported.

2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.

3) Requires inpatient hospitalization or prolongation of existing hospitalization.

4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5) Is a congenital abnormality or birth defect.

6) Is an important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the protocol, consent, or is not listed at the specificity or severity that has been observed.

Medical and Psychiatric History

A thorough medical and psychiatric history during the baseline phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or concerning signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through the final assessment. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to the IRB of record, per the IRB or record's guidelines.

Sites are required to enter reportable AEs and SAEs in data capture program. The AE form is used to capture reportable AEs and SAEs (as defined in the protocol) and will be reviewed by the study PI upon submission. Additional information may need to be gathered to evaluate SAEs and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event:

Grade 1	**Mild**	Transient or mild discomfort (typically < 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	**Moderate**	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study medication/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study intervention caused the event?

Reporting to the Data and Safety Monitoring Board

The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study intervention. The study medical clinician should consult with the lead investigator as needed. If necessary, a study medical clinician may suspend any trial interventions and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-study visit to assure safety and will be given recommendations for medical care and/or referrals to treatment, as necessary.

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