PRevention Of Methamphetamine Use among Postpartum Women Trial (PROMPT)
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PRevention **O**f **M**ethamphetamine Use among **P**ostpartum Women **T**rial (**PROMPT**)

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A. **Introduction**

While substantial attention and resources have been directed at the opioid epidemic in the US, another deadly drug epidemic – methamphetamine use (MU) – has evolved. Pregnant and postpartum women, particularly in the Mountain West are disproportionately affected by these twin epidemics. While most pregnant women achieve abstinence by late pregnancy, the postpartum period is a particularly vulnerable time.[1] Postpartum return to use is high and potentially deadly. Data from the Utah Perinatal Mortality Review Committee indicate that from 2005-2016, MU contributed to one out of every five deaths of pregnant and postpartum women; 85% of these deaths occurred in the postpartum period and, 70% of methamphetamine-related deaths also involved opioids.[2] While medications for opioid use disorder (OUD) reduce return to opioid use among postpartum women,[3, 4] similar interventions to reduce return to MU are lacking. Among postpartum women who used cocaine in pregnancy, micronized progesterone was associated with a reduction in cocaine use in the first 12 weeks postpartum in a randomized, placebo-controlled trial.[5] Reflective of high frequency of polysubstance use in this population, nearly half of the women in this trial had co-occurring OUD.

In this proposed study, we will assess feasibility, safety, and preliminary efficacy of micronized progesterone to decrease return to MU among postpartum women with MUD, defined as stimulant use disorder meeting Diagnostic and Statistical Manual of Mental Health Disorders V criteria with methamphetamines.[6] The study is a randomized controlled trial enrolling postpartum women with MUD. Participants will be randomized to 200 mg oral micronized progesterone twice daily or placebo for 12 weeks postpartum. The recruited cohort of postpartum women will be sufficiently large to determine feasibility, defined as achieving our enrollment goals in the study period, safety, defined as no difference in adverse outcome between groups and preliminary efficacy defined as decreased return to MU among women receiving progesterone compared to placebo.

Primary Objective: To determine feasibility, safety and efficacy of micronized progesterone for prevention of return to methamphetamine use among postpartum women with MUD.

B. **Background**

B1. Significance of Methamphetamine Use in the US

In the face of opioid epidemic, widespread MU among women has emerged as a deadly, and largely unaddressed, public health crisis in the Western United States.[7, 8] Women in the Mountain West (Utah, Nevada, Colorado, Idaho, Montana, Wyoming) have higher proportion of MU compared to women in other geographical areas in the United States (**Figure 1**).[9] Overall, men have higher rates of MU than women.[10] However, in the past decade, methamphetamine-related overdose deaths among women increased at a higher rate compared to men. Women's deaths also more frequently involve both methamphetamines and opioids.[11, 12] Yet, few interventional studies have specifically focused on addressing MU among women.

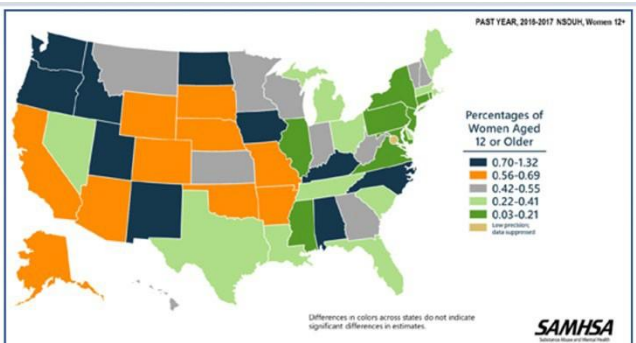


Figure 1: Methamphetamine Use among Women by State, 2016-2017; Substance Abuse and Mental Health Services Administration (SAMSHA)[3]

B2. Methamphetamine's Long-Term Consequences on Pregnant and Postpartum Women: The consequences of MU on this vulnerable population cannot be overstated; perinatal women with MU face increased risk of adverse maternal and infant adverse outcomes including severe maternal morbidity, maternal cardiac complications, preterm delivery and maternal and infant death.[13-15] MU is the **single most common indication** for which pregnant women seek treatment at federally funded drug treatment programs, and nearly three quarters of admissions occur in the West.[16] In the rural West, nearly 12,000 deliveries yearly are complicated by maternal amphetamine use, double the number of deliveries complicated by opioid use.[17] Postpartum women are increasingly using both opioids and methamphetamines, a dangerous and deadly combination.[2, 18, 19]

At the University of Utah's Substance Use in Pregnancy: Recovery, Addiction, Dependence (SUPeRAD) Specialty Prenatal Clinic, the only prenatal specialty clinic for pregnant and postpartum with substance use disorders in Utah, the majority of women have MUD, defined as stimulant use disorder meeting Diagnostic and Statistical Manual

of Mental Health Disorders V criteria with methamphetamines,[6] and nearly half have both opioid use disorder (OUD) and MUD. The SUPeRAD clinic is a specialty prenatal and postpartum clinic for women with substance use disorders (SUD) in all stages of recovery and is based within the University of Utah's Obstetrics and Gynecology Department, Maternal Fetal Medicine Division. Led by Marcela Smid (PI), dual board certified maternal fetal medicine and addiction medicine specialist, SUPeRAD is staffed by multi-disciplinary team made up of obstetric providers, addiction and mental health specialists, community collaborating partners, social workers and research staff. SUPeRAD is also the primary recruitment site for multiple research studies focused on improving evidence-based care for pregnant and postpartum women with SUD, including OUD and MUD (**see Section C1 for more detailed description of clinical and research infrastructure**).

B2. Postpartum Period Vulnerability to Cessation and Return to Drug Use

Mounting evidence suggests that the postpartum period is a particularly vulnerable time for women with any SUD.[2, 20, 21] While the vast majority (>80%) of women achieve abstinence during pregnancy, they are at high risk for return to use postpartum.[22, 23] Multiple postpartum triggers including exacerbation of underlying mood disorders by postpartum hormonal changes, destabilization of co-occurring SUD, and removal of child custody are associated with return to use, overdose, and death.[20, 21, 24, 25] The Utah Perinatal Mortality Review Committee reports that MU contributed to 21% of deaths of 176 pregnant and postpartum women from 2005–2016; 85% of these deaths occurred in the postpartum period and 70% of methamphetamine-related deaths also involved opioids.[2] Increasingly, national organizations including the American College of Obstetricians and Gynecologists, Substance Abuse and Mental Health Service Administration (SAMHSA), the Society of Maternal Fetal Medicine, and American Society of Addiction Medicine, identify MU as an endangerment to women and infants' health.[26-29] SAMHSA has emphasized that women's use of stimulants is profoundly impacted by hormonal changes, yet little is understood about these changes in pregnancy and the postpartum period.[30, 31]

B3. Hormonal Changes Impacting Drug Use among Female Animals and Women: Fluctuations in female hormone levels may place women at risk of addiction and increased return to use after periods of abstinence.[32-35] In animal models, females acquire behaviors of repeated self-administration of substances including alcohol, cocaine, nicotine, and opioids more rapidly than males.[32, 36, 37] Estrogenized female rats (lower relative progesterone) repeatedly self-administer of higher amounts of methamphetamine compared to male rats, while non-estrogenized (higher relative progesterone) female rats self-administer lower amounts compared to estrogenized females and males.[38] Female rats also exhibit increased sensitivity for drug-, cue-, and stress-induced reinstatement to methamphetamine compared to males; supplementation with allopregnanolone, a metabolite of progesterone, decreases these behaviors in female rats only.[39] Similar patterns of hormonal sensitivity and drug use patterns are also seen among women. Women in the luteal phase of the menstrual cycle (higher relative progesterone levels) are less likely to exhibit addictive behaviors compared to women in the follicular phase (phase with lower relative progesterone levels).[40-43] These findings suggest that periods of higher progesterone (e.g., pregnancy) may be protective against drug craving and use while period of lower progesterone (e.g., postpartum) place women at risk of return to drug use.

B4. Role of Progesterone and Allopregnanolone in Pregnancy and Postpartum: In pregnancy, progesterone and its metabolite allopregnanolone, levels increase throughout gestation (**Figure 2**). At the time of delivery, progesterone and allopregnanolone precipitously decrease to pre-pregnancy levels. High levels of allopregnanolone in pregnancy may decrease drug cravings and may partly explain high rates of abstinence from drug use during pregnancy.[5, 44, 45] Low allopregnanolone levels among pregnant and postpartum women are also associated with increased depression and anxiety symptoms, which may predispose women to return to drug use.[46-49] Brexanolone, an

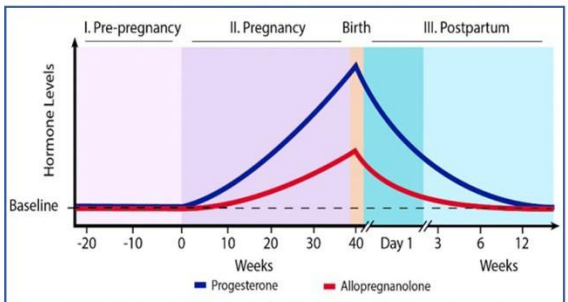


Figure 2: Progesterone and Allopregnanolone Levels during Pregnancy and Postpartum Period [Meltzer-Brody and Kanes (2020) *Allopregnanolone in postpartum depression: role in pathophysiology and treatment Neurobiology of Stress*]

intravenous formulation of allopregnanolone, is an effective treatment for severe postpartum depression and has been demonstrated to be safe in this population, including among breastfeeding women.[50]

B5. Progesterone as Novel Treatment for MUD among Women

Progesterone and allopregnanolone are often called “neurosteroids” as they easily cross the blood-brain barrier and regulate neuronal signaling.[51] Several clinical studies demonstrate that exogenous progesterone may serve as a novel intervention to reduce return to use among women including postpartum women (**Table 1**). Exogenous progesterone appears to be particularly effective among women to diminish drug cravings.[1, 51, 52] The proposed underlying mechanism is that exogenous progesterone increases allopregnanolone levels, which enhances GABA transmission and to attenuate drug reward.[53, 54]

Table 1: Randomized controlled trials of progesterone and substance use among women

Drug Type	Study Population	Treatment	Duration	Results	Authors
Amphetamine	18 women in follicular phase	200 mg progesterone/day vs. placebo	3 days	Progesterone increased positive subjective rating of drug	Reed at al 2010[53]
Cocaine	50 postpartum women	200 mg progesterone/day vs placebo	12 weeks	Less self-reported cocaine and longer time to return to use in treatment group	Yonkers et al 2014[42]
	10 actively using women	300 mg progesterone/day vs placebo	3 days	No difference in smoking cocaine did not differ between groups or craving	Reed et al 2011[54]
	10 women in follicular phase	400 mg progesterone vs placebo	Single dose	Subjective feeling of high attenuated in treatment group	Sofuoglu et al 2004[55]
	5 non-pregnant women	200 mg progesterone vs placebo	Single dose	Reduced subjective response in treatment group	Sofuoglu et al 2002[56]
Tobacco	41 postpartum women	400 mg micronized progesterone vs placebo	8 weeks	Higher proportion achieved abstinence Lower craving scores in treatment group	Forray et al 2017[41]
	46 postpartum women	400 mg micronized progesterone vs placebo	4 weeks	More median days until return to use in treatment group	Allen et al 2016[57]
	12 women who smoked	200 mg of micronized progesterone vs placebo	Single dose	Decreased cravings in treatment group	Sofuoglu et al 2001[58]

After oral administration, micronized progesterone, the proposed intervention, is metabolized by the liver to several steroids including allopregnanolone (**Figure 3**).

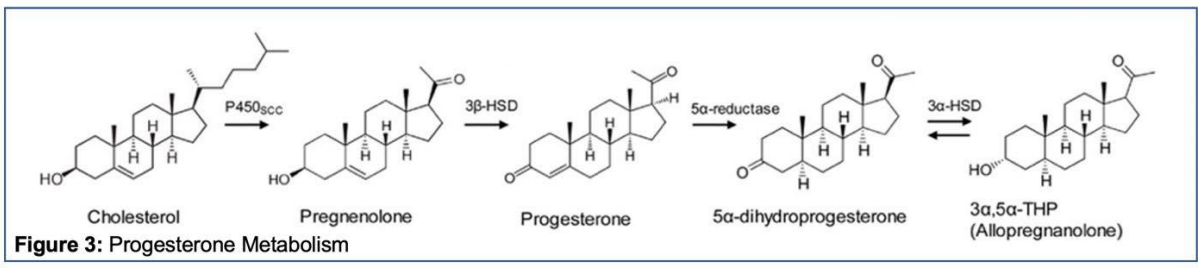


Figure 3: Progesterone Metabolism

B.6. Rationale for Proposed Study

Overall, findings to date suggest that progesterone has utility as a novel pharmacological treatment to prevent return to substance use among women. Most striking are data demonstrating that exogenous progesterone increases abstinence among postpartum women using cocaine or tobacco cigarettes. These findings suggest that progesterone may offer a potential treatment option to improve abstinence and prevent return to use, among postpartum women with MUD.

This proposed study focuses on MU among postpartum women, a population generally excluded from research protocols. It builds upon the promising results of progesterone to prevent return to use in other substance abuse disorders among postpartum women. Specifically, this study will explore the feasibility, safety, and preliminary efficacy of progesterone to prevent MU relapse, an intervention that has previously not been studied. Finally, the proposed study will also explore the association between allopregnanolone levels and methamphetamine craving. While others have examined progesterone levels and cocaine and tobacco cravings, allopregnanolone levels and methamphetamines cravings have not been previously explored.

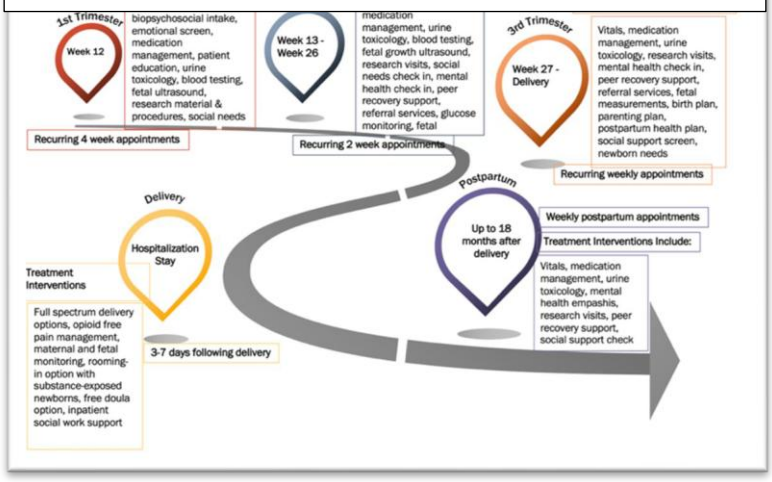
A total daily dose of 400 mg (200 mg twice daily) of oral micronized progesterone was selected, which reflects the same or similar doses used for prevention of return to substance use (cocaine, tobacco) among postpartum women.[5, 45, 55, 56] Dr. Forray's study of progesterone supplementation for prevention of return to tobacco use utilized 200 mg twice daily (400 mg total) and this dose was well tolerated for both mothers and breastfed infants. Additionally, a similar study for tobacco abstinence used the same dosing and there were no breastfeeding difficulties, depression or maternal or infant sedation (adverse events) reported in this study.[56] These studies demonstrate safety both postpartum women and breastfed infants. Approximately half of micronized progesterone is absorbed after oral administration with peak plasma levels with 2-3 hours and elimination half-life of 3-4 hours.[57] We propose to use twice daily dosing to maintain stable plasma levels.

C. SUPeRAD Clinical and Research Infrastructure

C.1. SUPeRAD Clinical Infrastructure

Each SUPeRAD clinic is staffed a multi-disciplinary team of health professionals with expertise in high risk obstetrical and addiction care, mental health professional, social workers, maternal newborn nurse care managers, peer recovery coaches, case managers and other ancillary services. As part of routine clinical care in the SUPeRAD clinic, women are monitored closely for substance use, depression, anxiety and sedation during pregnancy and the postpartum period up to 18 months (**Figure 4**).

Figure 4: SUPeRAD clinic patient flow by trimester and during postpartum period



Intensity of follow-up (weekly to monthly) is individualized by clinical necessity. Qualified mental health specialists (certified social workers, licensed clinical social workers, addiction specialists) are embedded into the workflow of the SUPeRAD clinic, assuring timely triage, evaluation and referral as appropriate, for women with mental health conditions or those with acute needs, including suicidal ideation. All postpartum women are scheduled for 1-2 weeks follow up after delivery and are screened for return to use, emotional well-being and sedation status. Prior to each SUPeRAD clinic, care conferences are attended by the entire clinical and research team. Medical history, including most recent substance use, medication for opioid use disorder (MOUD), mental health medications and mental health status, and lab value review, including urine toxicology, is part of every clinical visit, and discussion at care conference. These care conferences inform screening procedures including eligibility for available research protocols. All patients are seen by clinicians who are highly skilled in maternal mental health (see Appendix A). If psychiatric or outpatient referral is needed, direct linkage to care is the standard of care. Upon study completion, any research participants are eligible for all clinical care in SUPeRAD for up to 18 months postpartum.

C.2. PARCKA and OGRN Research Infrastructure

The research will be overseen by weekly study meetings, an external Data Safety Monitoring Committee, the University of Utah's Institutional Review Boards (IRBs) and the FDA. The success of this proposal and safety of participants will rely on the integration of SUPeRAD clinical and research infrastructures that are designed to recruit and retain pregnant and postpartum women and individuals with SUD in research protocols. The SUPeRAD clinic integrates research coordinators and assistants from University of Utah's department of Internal Medicine's Division of Epidemiology's Program for Addiction Research, Clinical Care, Knowledge, and Advocacy (PARCKA) and the Obstetrics and Gynecology Department's Obstetrics and Gynecology Research Network (OGRN) **(Box 1).**

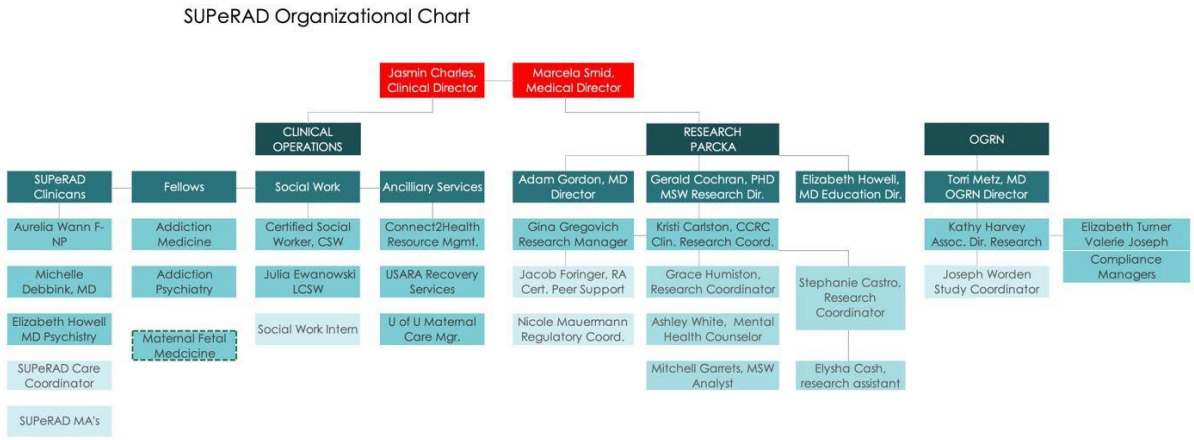
See Figure 5 for organizational chart and Appendix A for description and qualifications of clinical and research staff.

Box 1: University of Utah research infrastructures embedded within SUPeRAD clinic.

Program for Addiction Research, Clinical Care, Knowledge and Advocacy (PARCKA)
The mission of PARCKA is to promote and provide addiction-related clinical care, research, education, and advocacy to the University of Utah, the local community, and the nation. PARCKA conducts research examining the clinical, epidemiologic, health services, policy, and implementation science aspects of substance use and addiction. Dr. Cochran (Co-I) is PARCKA's Director of Research and Dr. Smid is core faculty within PARCKA.

Obstetrics and Gynecology Research Network (OGRN)
OGRN has developed an experienced research infrastructure with pregnant and postpartum women consisting of 1) a central administrative core that provides protocol development as well as IRB, compliance, human resource, and financial oversight for all active research protocols, and, 2) clinic research personnel in the five tertiary hospitals as well as the offices of over 120 women's health care providers, in the northern Utah urban corridor. The OGRN currently employs 51 clinical research personnel involved in recruiting and maintaining participation in a number of NIH-funded clinical research protocols.

Figure 5: SUPeRAD Clinical and Research Infrastructure Organizational Chart



Prior to each SUPeRAD clinic, research staff screen potential participants from available medical records for eligibility in research protocol. At care conferences, research staff are present at each care conference and study eligibility is reviewed with clinical staff every week. Potential participants are approached in SUPeRAD clinic, however, patients are not required to participate in any research protocol to receive care in SUPeRAD clinic. PARCKA and OGRN research team staff are trained and familiar with a variety of instruments for assessing substance use (including DSM-V criteria), mental health assessments (including the Columbia Suicide Severity Rating Scale, Edinburgh Postpartum Depression Scale and Generalized Anxiety Disorder – 7 tools). All research team members are trained to engage appropriate clinical triage and referral required for all study protocols. Because our research teams are specialized in both maternal health and substance use, research assistants and coordinators have the acumen and experience to assess for patient safety, even in unforeseen circumstances. They are facile in engaging the clinical infrastructure to appropriately contact clinicians and triage patients for health or safety concerns. For patients who are enrolled in study protocols, all University of Utah and SUPeRAD clinical services, including addiction and mental health care services, are readily available. In the event of mental health crisis, clinical and research staff follow established protocols to maintain safety (see **Figure 6**). Mental health status and medications are reviewed at each care conference for each patient, including those in research protocols. During care conferences, clinic or research visits or research team meetings, clinicians and research staff address concerns about oversedation or other symptoms, including dose adjustment, medication tapers or mental health or other referrals as appropriate. In the event of a continued or return to substance use, clinical staff discuss available treatment options and referrals to higher level of care as appropriate. SUPeRAD partners with variety of residential treatment programs and outpatient treatment programs in the region and we can facilitate timely assessment and admissions (**see Section H Appendix B)**. Through these partnerships, we are able to maintain clinical and research continuity with research participants.

D. Study Design

D.1. Primary and Secondary Objectives

The Primary Objective of this study is to assess feasibility, safety, and preliminary efficacy of micronized progesterone to decrease return to methamphetamine use among postpartum women with methamphetamine use disorder. We hypothesize that the **PR**evention **O**f **M**ethamphetamine Use among **P**ostpartum Women **T**rial (**PROMPT**) will be feasible, defined as achieving our enrollment goals in the study period and safe, defined as no difference in adverse outcome between groups. We further hypothesize that the PROMPT study will demonstrate preliminary efficacy defined as decreased return to MU among women receiving progesterone compared to placebo.

The Secondary Objective is to evaluate the association between salivary allopregnanolone levels and methamphetamine craving in control and treatment groups using a validated and reliable stimulant craving questionnaire. We propose collecting salivary levels of allopregnanolone obtained at delivery, two days postpartum, and every other week up to 12 weeks postpartum. We hypothesize that postpartum women with higher salivary allopregnanolone levels will have lower methamphetamine craving scores.

We will recruit 40 postpartum women with methamphetamine use disorder who have achieved abstinence from methamphetamine and other substances for at least 4 weeks. Enrolled participants will be randomized to 400 mg (200 mg twice daily) oral micronized progesterone daily or placebo. We will focus on women with MUD, as opposed to those with sporadic use, as they are at the highest risk of return to use. Because many women with MUD have co-occurring OUD, we will include women with OUD in remission. Once randomized, the participant will participate in seven study sessions over a 12-week period.

D.2. Screening Procedures

All patients who present for prenatal care at the University of Utah's SUPeRAD or other prenatal clinics are eligible for screening. We anticipate that the vast majority of recruitment for PROMPT will occur at SUPeRAD as it is the main referral site for pregnant and postpartum women with a substance use disorder in our health system and in the

region. Research participants, receiving care from other providers, are able to utilize the clinical resources of SUPeRAD. We may also provide information about the PROMPT trial to our partnering agencies for referral to research coordinators including local methadone clinics, residential treatment programs for pregnant and parenting women and local addiction medicine and psychiatry treatment specialists. Research assistants (RA) will screen and approach women who are pregnant at their second SUPeRAD visit or recently postpartum (within twelve weeks of delivery) for eligibility. Women may be consented during pregnancy, although study interventions will not occur until after delivery. If a potential participant appears to meet the criteria for enrollment and expresses interest in the study, she will be told about the study and asked to sign the informed consent form. A copy of the consent form will be provided to the participant. After delivery, women will be randomized. Collateral contact information will be collected using the Locator Form. Because 78% of women with MUD in the SUPeRAD clinic have co-occurring OUD, we will include women with OUD in remission for four weeks, defined as no self-report of opioid use and expected urine toxicology. Unexpected opioid use will be defined as urine toxicology results consistent with opioid use other than expected medications (methadone, buprenorphine, or prescribed medication).

D.3. Eligibility Criteria

Must meet all of the following **Inclusion Criteria**:

1. Diagnostic and Statistical Manual V (DSM-V) criteria of any severity for substance use disorder of methamphetamine in the six months prior to conception, during pregnancy or within 12 weeks postpartum
    a. Cravings, urges and dreams of use are included as symptoms of the substance use disorder. These can occur in the absence of active use.
2. No active methamphetamine use at time of enrollment or within past 4 weeks prior to enrollment by self-report or urine toxicology.
3. If diagnosis of *active* OUD, defined as self-report or urine toxicology consistent with non-prescribed opioids in past six months, must be on stable dose of medication for OUD (methadone, buprenorphine, naltrexone) for two weeks prior

to enrollment in order to allow for postpartum dose adjustments. No misuse of opioids at time of enrollment or within past 4 weeks prior to enrollment by self-report or urine toxicology.

   a. Prescribed opioids for pain management for surgical or medical procedures including birth are acceptable if ≥ two weeks from enrollment.

4. Intrauterine device, barrier method or permanent female sterilization (e.g. tubal ligation) for contraception during the study period
5. End of pregnancy within past 12 weeks
6. Residing within 100 miles of study site
7. No plans to move more than 100 miles from study site within study period
8. Have phone and/or able to provide collateral contact information for two individuals
9. Ability to provide informed consent
10. Stable on allowable psychiatric medications including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mood stabilizers for four weeks prior to enrollment

Cannot meet any of the following **Exclusion Criteria**:

1. Major medical illness in which progesterone may be contraindicated (significant liver disease, history of thrombophlebitis, stroke, heart disease, suspected or known malignancy, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders) per PI and/or study clinician assessment.
2. Any of the following laboratory abnormalities (within 2 weeks of screening and enrollment)
   a. Active hepatic dysfunction defined as aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than twice the upper limit of normal or clinical evidence including ascites or jaundice
   b. Anemia defined as hemoglobin less than 8 g/dL indicating anemia
   c. Renal impairment defined as creatinine greater than 2.0 mg/dL
   d. Hypothyroidism defined as TSH greater than 5 mIU/L
3. Abnormal vital signs at baseline visit
   a. Temperature < 97 or > 100.3 degree Fahrenheit

b. Pulse < 50 and > 130
c. Blood pressure (BP) greater than systolic BP ≥ 160 or ≤ 80 and diastolic BP ≥ 110 or ≤ 50
d. Oxygen saturation < 92%
e. Respiratory rate < 9 or > 30

4. Allergy to micronized progesterone or ingredients in placebo including peanut oil, gelatin or cellulose
5. Self-reported progestin-containing oral or depot containing contraceptives intolerance.
6. Do not speak English or Spanish
7. Taking potent inhibitors of CY P450 3A4 including clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil and goldenseal.
8. Severe depressive symptoms defined as Edinburgh Postpartum Depression Scale (EPDS) score of ≥ 19 or severe anxiety defined GAD ≥ 15 at time of enrollment.
9. Active suicidality defined as expressing current thoughts of self-harm verbally to study clinician or study team member, Colorado Suicide Severity Rating Scale score > 0, or EPDS Question #10 score of greater than 0
10. Current psychosis, history of psychiatric hospitalizations for psychosis or suicide attempt within the past six months or past suicide attempt without hospitalization within the past six months
    a. Past history of suicidal ideation alone or self-harm (e.g. cutting) with no plan for suicide are not exclusionary
    b. Hospitalization for management of substance use disorder and its sequelae is not exclusionary
11. Current or known pending incarceration
12. Active alcohol use disorder within past six months
13. Use of the following concomitant drugs, supplements and over-the-counter medications in the two week prior to enrollment: stimulants, barbiturates, benzodiazepines, non-benzodiazepine hypnotics, orexin antagonists, first

generation anti-histamine, herbal sedatives, methaqualone and analogues, skeletal muscle relaxants, opioids (other than methadone or buprenorphine), anti-psychotic medications, certain anti-depressants or other medication with significant sedative properties as evaluated by the PI and/or study clinician. See **Appendix C** for full list of excluded medications.

14. Progestin containing medications including oral hormonal contraceptive methods, vaginal ring, contraceptive patch, injectable or implant.

In order to assess medical eligibility criteria for enrollment into the study, the PI and/or study clinician will review the participant's medical history, medications and laboratory values from the patient electronic medical record. For purposes of the study, moving is defined as relocating more than 100 miles away from the study site. If labs within two weeks of baseline visit are not available, a complete blood count, comprehensive metabolic panel and a thyroid stimulating hormone (TSH) will be obtained and reviewed for eligibility criteria. All SUPeRAD patients have standard physical exams, vital sign review and lab values completed at each clinical visit, as appropriate. Review of these data will be utilized to determine participant eligibility. If stigmata of major medical conditions are present (ascites, jaundice, shortness of breath and vital signs concerning for pulmonary embolism, unilateral leg swelling, etc.), immediate evaluation and triage of patient will occur and enrollment into the study will not be performed unless identified or suspected major medical conditions have resolved.

With respect to maternal mental health, similar to Yonkers et al study,[5] we will not exclude women with mental health conditions. However, as described in Section D.6.iii Study Visits, the PI and/or study clinician will evaluate a patient medical and mental health history, medication and mental health status. In the event of depression or anxiety symptoms and/or co-occurring mental health, clinicians will 1) offer mental health treatments with the SUPeRAD clinical structure 2) offer all participants with co-occurring mental health conditions or symptoms referral to psychiatric care within the health care system and facilitate that referral through a warm hand-off and 3) discuss with potential participants the risks and benefits of enrolling in the study, including potentially deferring enrollment until mental health stabilization and other eligibility criteria are met.

Women with nicotine use disorder will be included and offered standard of care for tobacco cessation including nicotine replacement treatment and behavioral interventions through the Utah Department of Health Quit Line (https://livingwell.utah.gov/docs/bhpguide/bhpGuide_QuitLine.pdf).

D.4. Informed Consent Procedures and Documentation

Written informed consent will be obtained before entry into the trial including full disclosure of the nature and potential risks of participating in the trial. Women will be provided verbal and written informed consent obtained in English or Spanish; if they are not fluent in either of these languages, they will not be included.

D.5. Randomization Procedures

Randomization will occur 1:1 in the PROMPT study. To address presence of OUD, we propose a stratified random assignment with block sizes of four within strata. The two strata will be: **1)** presence of OUD, or **2)** no OUD. The study statistician will generate a randomization list that includes study participant numbers and treatment condition. To maintain that the entire study team remains blinded to allocation, we will utilize the University of Utah's Investigational Drug Service (IDS)

D.6. Study Procedures

D.6.i. Study Drug Dispensation

A total daily dose of 400 mg (200 mg twice daily) of oral micronized progesterone will be utilized for the active medication. Oral micronized progesterone and similar-appearing capsules (placebo) will be prepared by the University of Utah Investigational Drug Service (IDS) Pharmacy. We utilize commercially available micronized progesterone (NDC 17478-0766-10, Akorn, Inc). For the active investigational drug, IDS staff will over-encapsulate the active 100 mg micronized progesterone capsules using empty gelatin capsules made by Capsulin (https://capsuline.com/products/colored-gelatin-capsules-size-000-white-white-f00153-p) and hand pack with microcrystalline

cellulose (https://www.letcomedical.com/avicel-ph-105-848) until fully filled. For the placebo capsules, the IDS staff will hand pack empty gelatin capsules with microcrystalline cellulose until fully filled. Each batch is given a lot and expiration based on a year from compounding or sooner if the ingredients expire before that date.

Study drug dispensation will occur in partnership with the IDS, which is a function of the Department of Pharmacy. The IDS provides support to ensure the safety and efficiency of trials at University of Utah Health that use investigational product/investigational drug. IDS will prepare study-specific information to help other pharmacists handle, inventory, and control investigational drugs. The IDS pharmacists will ensure that the investigational drugs are handled according to state and federal laws and regulations, hospital policy, Institutional Review Board (IRB) policy, and sponsor protocols. Pharmacy personnel that perform investigational drug accountability at UUH satellite locations approved for conducting research protocols are considered an extension of the IDS.

For each full study visit (baseline, weeks 2,4,6,8,10), study medications will be distributed. At enrollment, the RA will provide the IDS the next participant number for randomization and will obtain a 2-week supply of study mediation from the IDS pharmacy. At each subsequent study visit, the IDS will receive the drug order for study medications and mark the bottle with sequentially numbered containers. The RA will then provide the participant with study medication. Any unused medication will be obtained from participant and returned to IDS at each study visit. As this is a double-blinded trial, neither the research assistant, other study staff or the participant will know allocation group. Participants may choose to use a dosing calendars to record medication adherence. Missed doses will not be considered deviations.

D.6.ii. Randomization and Baseline

Research staff will screen participants for eligibility starting at their second SUPeRAD visit and up to 12 weeks postpartum; if consented while pregnant, eligibility procedures, enrollment and randomization will not occur until postpartum. Once screened and consented, participants will complete baseline assessments prior to randomization to

ensure that participant status has not changed. Once a participant is consented and enrolled, the study team will schedule weekly study visits (7 days +/− 3 days) for 12 weeks (see **Table 2**). These are target windows. If the participant cannot be seen within these windows, she should be seen as soon as possible. A delayed, missed, or partial visit will not be considered a protocol deviation. Full study visits will occur at weeks 2, 4, 6, 8, 10, 12 in a private clinic or research room. Participants will complete study assessments on an iPad or paper or over the phone. Participants will provide urine and salivary samples. This visit is anticipated to last approximately 30-60 minutes. Participants who are unable to complete a full study visit in person may complete the questionnaires over the phone or virtually. Study coordinators are encouraged to work with participants to complete as many assessments as possible for each timepoint. Partially completed visits and missed assessments will not be considered deviations.

Phone or virtual visits will occur weeks 1,3,5,7,9 and 11 unless study participant prefers in-person visits. Home or off-site visits may be arranged with the study participant to facilitate study collection. RA may arrange to meet participants in public areas or in their home. They will have phone availability at all times to ensure safety of the RA. Alternative COVID-19 procedures will be instituted if necessary (reviewed on page 25). At randomization, we will collect medical and obstetric history, concomitant medication and supplement use from the medical record. Self-reported information will be confirmed with the medical record.

Participants will be recruited and enrolled within twelve weeks of delivery for participation in this study. Participants will be instructed to take their first dose the evening of receiving study medication and then take twice daily in the morning and evening as close to 12 hours apart (ideally 12 +/- 2 hours) with food for the next 12 weeks.[56] Research team members will recommend that the participant should take study medication with food. Doses outside of the window are not considered deviations, but will be recorded as this is a feasibility trial. If participants are enrolled and are immediately postpartum, study medications will not be initiated until four days postpartum, as breastmilk is most often established by this time.[58] Administration of progesterone earlier than four days can inhibit prolactin and thereby affect breastmilk production.[59] Participants who are lactating will perform a self-assessment of breastfeeding using the Bristol Breastfeeding Assessment

Form administered interview style by the RA.[60] If participant reports delayed onset of lactation, medication start date will be postponed until breastmilk production is established or participant is no longer breastfeeding (but still within twelve weeks of delivery). If participant does not plan to breastfeed, the assessment will be waived and medications will start on postpartum day 4 or thereafter.

D.6.iii. Study Visits

At each study visit, the RA will collect study measures and samples outlined in Table 2.

Table 2: Timeline of questionnaires and assessment

Time point Week	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Medical History, Medications & Lab Review	✓												
DSM V Checklist	✓												
SCQ-Brief	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bristol BAF	✓												
SuCal (28 days prior to baseline visit)	✓												
SuCal (7 days prior or since last visit)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Administration of study medication	✓		✓		✓		✓		✓		✓		
Pill count of returned med			✓		✓		✓		✓		✓		✓
C-SSRS (2 weeks prior to baseline visit)	✓												
C-SSRS Since Last Visit		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GASE Side effects		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IBSA		*	*	*	*	*	*	*	*	*	*	*	*
Breastfed Infant chart review		*	*	*	*	*	*	*	*	*	*	*	*
EPDS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GAD-7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBC, CMP, TSH [A]	✓												
Salivary sample	✓		✓		✓		✓		✓		✓		✓
Urine pregnancy test	✓						✓						✓
Urine toxicology	✓		✓		✓		✓		✓		✓		✓

DSM V = Diagnostic and Statistical Manual V; SCQ-Brief = Stimulant Craving Questionnaire; Bristol BAF =Bristol Breastfeeding Assessment Form; SuCal = Substance Use Calendar; C-SSRS Colorado – Suicide Severity Rating Scale GASE = Generic Assessment of Side Effects; IBSA = Infant Breastfeeding and Sedation Assessment; EPDS = Edinburgh Postpartum Depression Scale, GAD 7 = Generalized Anxiety Disorder 7

✓= will be collected at each visit

** = will be collected as needed for breastfed infants only*

[A] = if results not available 2 weeks prior to enrollment

Baseline visit

At the baseline visit, we will collect the Diagnostic and Statistical Manual V checklist, stimulant craving questionnaire (SCQ-Brief), Colorado Suicide Severity Rating scale, Bristol Breastfeeding Assessment form, Substance Use Calendar, depression screening using the Edinburgh Postnatal Depression Screen (EPDS), anxiety screening using the

Generalized Anxiety Disorder (GAD-7). We will also collect blood (as needed), urine pregnancy test, urine toxicology and a salivary sample.

- At baseline visit(s), a full medical and lab review will occur by the PI and/or study clinician to determine eligibility as outlined in Section D.3. As detailed below, mental health assessments will be reviewed including EPDS, GAD-7 and C-SSRS and participant's current engagement in mental health will be assessed, including prescriptions for psychotropic medications. Qualified mental health providers/medical clinicians (see Appendix A) are available at each clinical and study visit for evaluation, triage, treatment and referral. As described below, we will follow established protocol to offer appropriate treatment and referral to appropriate mental health care. For those individuals who have moderate depression or anxiety, the study PI will discuss risks and benefits of participating in a research study in which progesterone may increase depressive symptoms. We will also review that in the three other studies with postpartum women, depressive symptoms were not increased with this dose of progesterone in women with cocaine use disorder[5] and tobacco use disorder.[45, 56] Women with underlying mental health conditions were not excluded from these studies.
- C-SSRS score > 0 indicates suicidal ideation (yes for Categories 1-5) or behavior (Categories 6-10). During screening, women will not be eligible for participation if they screen positive for suicidal ideation or behavior. If at the baseline visits, C-SSRS score > 0, research team will implement our Quick Suicide evaluation protocol (Figure 6) which include notification of PI and/or study clinician and triage as appropriate to mental health professional, emergency room and/or mobile crisis unit. All of the research staff are trained and familiar with this algorithm. Study medication will be deferred until clinical stabilization has occurred and all study criteria have been met.
- EPDS score of ≥ 19 represents severe depression and GAD ≥ 15 indicates severe anxiety symptomology. Prior to the baseline visit, potential participants with severe symptomology will be excluded from participation. However, if after consent, enrollment and randomization, baseline assessment indicates severe depression or anxiety symptomology, research coordinators will notify the PI and/or study clinicians

and the participant will be evaluated by a qualified mental health practitioner (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation) either in person or by phone if not on site on the same day. Appropriate triage will occur with study clinician and/or PI for timing and urgency of referral to offer initiation of medication, medication adjustment and/or referral to maternal mental health therapist or psychiatrist referral, emergency room evaluation will be arranged, as appropriate. If higher level of care is warranted, qualified mental health clinicians will initiate evaluation through the Huntsman Mental Health Institute clinical assessment line (801-587-3190). Treatment options offered will include psychotropic medication, medication adjustment and/or maternal mental health therapist or psychiatrist evaluation and referral will be arranged, when and as clinically appropriate (see Appendix A for on-site qualified mental health professionals available for referral). Appropriate triage will occur with study clinician and/or PI for appropriate timing and urgency of referral, as appropriate. We will defer initiation of study medication until depression and anxiety symptoms have improved EPDS < 19 and GAD7 < 15 and other study criteria have been met.

- An EPDS score of 14-19 indicates moderate depression and GAD7 10-14 indicates moderate anxiety. For participants with this symptomology, they will not be excluded or withdrawn from the study. However, research assistants will notify the PI and/or study clinicians and the participant will be evaluated by a qualified mental health practitioner (see Appendix A for clinical and research personnel qualifications) at the baseline visit. Treatment options offered will include medication initiation, medication adjustment and/or maternal mental health therapist or psychiatrist evaluation and referral will be arranged, when and as clinically appropriate. Appropriate triage will occur with study clinician and/or PI for appropriate timing and urgency of referral, as appropriate and clinically indicated (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation). With respect to study medication, a risk-benefit discussion for progesterone treatment will occur between participant and PI and/or study clinician.

15. Psychiatric medications, specifically SSRI, SNRIs and mood stabilizers, will not be an exclusion for participation with exception to those mentioned in the Eligibility

Criteria (Section D.3). However, participants will need to be on a stable dose for four weeks prior to enrollment.

Subsequent study visits

At each subsequent full study visit (weeks 2,4,6,8,10,12), all participants will be assessed for substance use using the Substance Use Calendar (SuCal), stimulant craving (SCQ-Brief), depression (EPDS), and anxiety (GAD-7). Breastfeeding participants will complete the Infant Breastfeeding and Sedation Scale (IBSA). Urine and salivary samples will be obtained. We will also perform an investigational product pill count, and assess side effects using the Generic Assessment of Side Effects (GASE).

The EPDS, GAD7 and the GASE assessments contain elements assessing emotional wellbeing including irritability, agitation, nervousness, depressed mood and suicidality. The GASE scale specifically includes questions to determine if these symptoms are related to the study medication. The GASE also includes an assessment of fatigue/loss of energy (sedation) with questions regarding relationship to study medication.

Each week that a full study visit is not conducted (weeks 1,3,5,7,9,11), the research participant will be contacted by the research assistant to complete an EPDS, GAD7, GASE and IBSA assessment. If on the EPDS question #10, the participant indicated an answer greater than 0 (no thoughts of harm) or GASE >0 “thoughts of suicide”, the C-SSRS Since Last Visit will be administered and clinical protocol (Figure 6) will be followed. This may be conducted over phone, text, virtual visit or in-person per the study participant’s preference. If any side effect is reported to be severe, research assistants will contact the PI and study clinicians as described in section D.7.i and immediate triage will occur as appropriate. For any suicidality reported (EPDS Question 10 or C-SSRS Since Last Visit answer >0), the research assistant will utilize **Figure 6** (Quick Suicide Safety Screening guide). For any response of “no” to IBSA Question 1b or “yes” to IBSA Questions 1 c-d, the research assistant will advise PI and study clinician and direct participant to nurse in pediatrics for triage and evaluation.

- A EPDS score of ≥ 19 indicates severe depression symptomatology and GAD ≥ 15 indicates severe anxiety symptomatology. Research assistants will notify the PI and/or study clinicians immediately (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation). and the

participant will be evaluated by a qualified mental health practitioner either in person or by phone if not on site on the same day. Appropriate triage will occur with study clinician and/or PI for appropriate timing and urgency of referral to offer initiation of medication, medication adjustment and/or referral to maternal mental health therapist or psychiatrist referral, emergency room evaluation will be arranged, as appropriate. If higher level of care is warranted, qualified mental health clinicians will initiate evaluation through the Huntsman Mental Health Institute clinical assessment line (801-587-3190). PI and/or study clinician will also evaluate participant to determine association with study medication. See section D.7.i for dose adjustment guidelines if study clinicians determine that symptoms are likely attributable to study medication. If associated with study medication, this will be reported as a serious adverse effects and reviewed with the DMC (see Section D.6.iv.).

- If EPDS Question #10 or C-SSRS Since Last Visit >0 (Table 2) and a provider will be notified for immediate evaluation and follow Figure 6 protocol for emergency department evaluation. If active suicidality is noted after enrollment, a provider will make an immediate assessment and referral for evaluation per study protocol (see Figure 6). If associated with study medication, this will be reported as an serious adverse effects and reviewed with the DMC (see Section D.6.iv.).
- An EPDS score of 14-19 indicates moderate depression and GAD7 10-14 indicated moderate anxiety. Research assistants will notify the PI and/or study clinicians and the participant will be evaluated by a qualified mental health practitioner (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation) 24 hours. Treatment options offered will include medication initiation as appropriate, medication adjustment and/or maternal mental health therapist or psychiatrist referral will be arranged (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation). If the patient is in existing treatment, we will continue to monitor her depression and/or anxiety and notify her treatment professional on symptoms. See section D.7.i for dose adjustment guidelines if study clinicians determine that symptoms are likely attributable to study medication. If associated with study

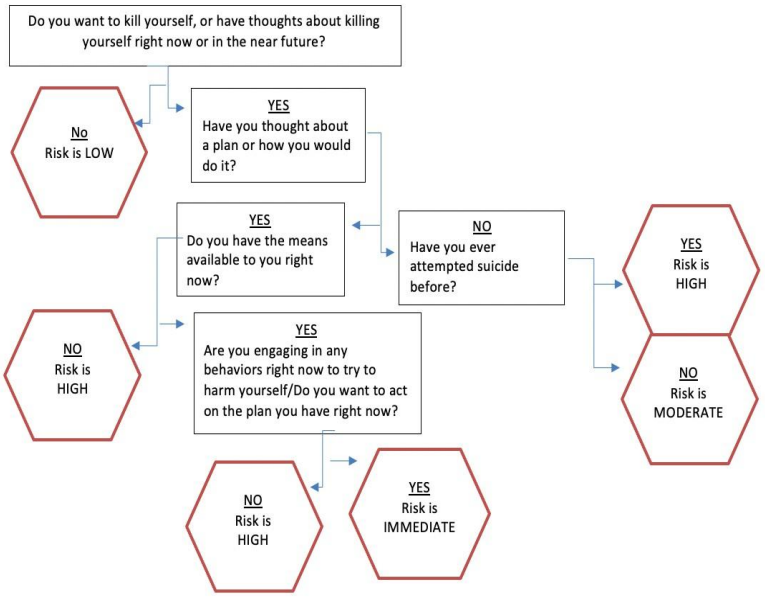
medication, this will be reported as an serious adverse effects and reviewed with the DSM (see Section D.6.iv.)

- If participant answers GASE = severe for any side effect (except suicide, see above section), research assistants will contact PI and/or study clinicians immediately (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation). Participants will then be contacted regarding side effects and appropriate plan for evaluation will be made. If GASE = mild or moderate on any side effect, RA will determine participant's desire to be called or seen by study clinician, including depressed mood, anxiety, agitation, nervousness, sedation or irritability. If participant desires to address concerns, research coordinators will contact study clinician and a clinical determination will be made for most appropriate triage (phone, video, same day appointment, urgent care, emergency room). At end of each study visit, RA will emphasize that symptoms were to develop in between study visits, participants can contact the study phone and similar triage mechanism would be implemented. See section D.7.i for dose adjustment guidelines if study clinicians determine that symptoms are likely attributable to study medication or participants deem the side effects intolerable. See section D.7.iv for additional Adverse Event Reporting guidelines.
- In the event of return to use reported by the participants, research coordinators will contact the PI and/study clinicians for assessment and referral to higher level of care (see Appendix B for list of community substance use treatment partners including outpatient treatment programs and residential treatment programs targeted at parenting individuals).
- In the event that the research coordinators are concerned about worsening emotional well-being, return to use or a request for evaluation regardless of EPDS, GAD7 and GASE responses, the RAs will contact the PI and study clinician for evaluation and triage within 24 hours (see Appendix A for on-site physicians and qualified mental health professionals available for referral and evaluation)..

As mentioned above, routine clinical care in the SUPeRAD clinic includes monitoring, triage and evaluation for substance use, depression, anxiety and sedation during pregnancy and

the postpartum period. Irrespective of study participation, women have follow-up at 1-2 weeks postpartum, are screened for return to use, emotional well-being and sedation status. Intensity of follow-up (weekly to monthly) is determined by clinical necessity and qualified mental health specialists (certified social workers, licensed clinical social workers, addiction psychiatrists) are embedded into the workflow of the SUPeRAD clinic.

Figure 6: Quick Suicide Screening Guideline
Ask these questions if participant scores > 0 of EPDS Question 10 or > 0 on Colorado Suicide Severity Rating – Scale or C-SSRS Since Last Visit



RISK LEVEL	ACTION
Low	1. Give patient resources (e.g., UNI Crisis Line) 2. Inform PI and medical provider(s)
Moderate	1. Contract for safety with patient & schedule call back within 2 hours 2. Inform PI and medical provider(s) 3. Call back patient at scheduled time and discuss treatment recommendations
High	1. Contract for safety with patient & schedule call back within 1 hour or keep patient on phone 2. Contact UNI/MCOT ASAP 3. Inform PI and medical provider(s) 4. Discuss treatment recommendations with patient
Immediate	1. Keep patient on phone 2. Call 911 3. Follow instructions of 911 4. Inform PI and medical provider(s)

Potential risks for this study are low. Possible risks may include minor physical discomfort while collecting the weekly urine and salivary samples and completing the computer-based assessments. Additional risk related to potential side effects from the micronized progesterone are described below. Because depression is a known risk of micronized progesterone, we will assess EPDS and suicidality. The research assistants will review the GASE and EPDS at each study session where it is completed. If answer to question #10 on EPDS greater than 0 or the GASE suicidality question is ≥ 0 , the RA will utilize the following Quick Suicide Safety Screening Protocol (**Figure 6)** developed to have a uniform and expeditious response to a research participant at risk of self-harm.

Potential Side Effects of Micronized Progesterone

More common (> 5%)

- Dizziness
- Breast tenderness
- Headache
- Abdominal pain
- Fatigue
- Viral infection
- Abdominal distension
- Musculoskeletal pain
- Emotional lability
- Irritability
- Upper respiratory infection

Less common (<5%)

- Less breastmilk production
- Dry mouth
- Anxiety or depression
- Constipation
- Hypertension
- Bile duct blockage
- Skin rash
- Allergic reaction
- Acne
- Urinary tract infection
- Abnormal liver function
- Deep vein thrombosis or pulmonary embolism

Research assistants will review the GASE tool at each visit and will be trained to recognize symptoms of the less common, but serious, side effects including jaundice, severe abdominal pain, leg swelling or allergic reaction. The research assistants will notify the PI immediately who will review symptoms and triage the patient for further medical evaluation as appropriate.

Infant and breastfeeding monitoring

For those infants who are breastfeeding, infant monitoring will occur through maternal report and weekly chart review as needed (see Section D.6.iv) for adverse and severe adverse events. We will utilize the INC Neonatal Adverse Event Severity Scale to report infant adverse events.[61] If at baseline, participant indicates intention to breastfeed, a Bristol Breastfeeding Assessment form[60] will be completed as described in Section

D.6.i. If breastfeeding is initiated, research assistants will administer the IBSA at each study visit. Additionally, study participants will be asked if breastmilk volume is perceived as adequate or inadequate. If participant has concerns regarding breastmilk production, we will arrange an appointment with the University of Utah lactation consultants (801-213-4500). If participants answer yes to questions 1b-d, research assistants will advise and facilitate participants to contact the infant's pediatrician immediately and will contact PI and/or study clinicians immediately (see Appendix A for PI and/or study clinicians).

D.6.iv. Adverse Events

Maternal and breastfed infant adverse events (AEs) will be collected from when the participants begins taking the study medication until 24 hours after final dose of study medication (elimination half-life of oral progesterone is 5-10 hours). We will record reported symptoms from the GASE-D after enrollment but prior to the start of study medications. Maternal and infant medical records will be reviewed regularly during study participation. Birth/neonatal outcomes will be abstracted from the medical record. These outcomes include head circumference, weight and length at birth, gestational age at delivery, 1 and 5 minute APGAR scores, major birth defects, neonatal death, admission to NICU and need for resuscitation. We will record maternal and infant AEs and serious adverse events (SAEs) including:

- All deaths that occur in either the mother or the infant (SAE)
- All AEs/SAEs while on study drug.
- Maternal or infant hospital re-admission within 12 weeks of delivery (SAE)
- Any maternal or neonatal ICU admission within 12 weeks of delivery (SAE)

Participant reported side effects collected weekly via GASE-D will be recorded as Adverse Events:

- Mild side effects will be recorded as AEs only if they are determined to be AEs by the investigator during their review and assessment
- Any moderate and severe side effects, see D.7.i for dose hold criteria.

For participants who discontinue study medication prior to week 12, we will record AE's up to 24 hours after the final dose of study medication. Participants may continue completing study assessments. GASE-D responses will continue to be tracked but will not be recorded as AEs. SAEs will be recorded through the entire study duration.
For participants and breastfed infants, AEs including serious adverse events (SAEs) will be summarized by organ class and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities) and the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf). AEs and SAEs will be followed through resolution via chart review or phone call with maternal participant, whichever is appropriate to that event. Ongoing AE's at time of study completion will be closed with the end date of 24 hours after last dose of study medication. AEs will be presented as the number and proportion of participants experiencing at least on incidence of each event and will be presented overall and by treatment group. Listing of SAEs will be provided, sorted by treatment, system organ class and preferred term. Detailed in these listing will include severity, relationship to study drug and outcome. The number of participants experiencing each type of AE and SAE may be compared between treatment arms using either Fisher's Exact test or Pearson's chi-2 test, as appropriate. For breastfed infants, events will be summarized in a similar way, however infant death and other SAEs in breastfed infants are reportable.

Events will be reported to the local IRB per institutional procedures and the participating investigators and FDA, as required. Details of monitoring, documentation and reporting SAEs will be documented in the study's safety monitoring plan. Weekly communication will occur until study completion. Data monitoring for this study will be conducted by the University of Utah's Clinical Research Support Office (https://ctsi.utah.edu/crso). CRSO provides expertise, guidance and support to investigators, reviewing, developing and tracking protocol with FDA INDs.

D.6.v. Specimen Collection

Maternal urine and salivary samples will be collected on seven occasions by a health care provider or research staff trained.

Salivary samples

- After progesterone dosing (dosing to occur prior to study) approximately 5 ml of saliva will be collected into a tube. Processed samples will be stored frozen at -80°C for up to 3 months until the time of analysis.
- Under the direction of Diana Wilkins, PhD, Associate Director of the University of Utah's Center for Human Toxicology, saliva samples will be processed using a highly sensitive enzyme immunoassay for allopregnanolone levels validated for both serum and salivary samples (AssayPro, St. Charles, MO).
- We will process each sample twice and batch process the saliva samples every other month to avoid stability issues for stored saliva samples and kit expiration dates. We estimate that 15% of samples will need triplicate analysis due to: a) initial two sample difference of >10%, b) failed batch quality control, or c) need for dilution to obtain accurate quantity

Urine samples

8 mL of urine (4 mL minimum) will be collected at each study visit.

- The urine toxicology test is a 2-step process: first, an immunoassay for the qualitative detection of substances including amphetamines, opiate, buprenorphine, methadone, oxycodone, benzodiazepines using the E-Z Integrated Key Cup II or Inc. 14 Panel – Instant Drug Test CUP II.
- toxicology panel; sensitivity and specificity of all substances > 95%.
- A confirmatory test using mass-spectrometry is reflexed to quantify amphetamines, cannabinoids, opioids (including oxycodone, methadone, or buprenorphine), benzodiazepines, and their metabolites.

COVID-19 Alternative Procedures. In the event research participants are unable to be seen at the clinic due to pandemic concerns, or a participant becomes infected with the COVID-19 virus, the study team will follow the University of Utah's Vice President's for Research guidance for all research related study procedures available on their website: research.utah.edu. Participants will be able to complete the dosing, biological sample

collection and surveys from their home and can meet study personnel at appropriate community locations or at their homes. 24-hours prior to study visits, study staff will contact the participant to ask current risk questions determined by the CDC. If symptomatic, the study visit will be rescheduled as a virtual visit. If asymptomatic the study visit will occur as scheduled. research personnel will take universal precautions for risks with participants who are a person under investigation (PUI) or known COVID positive. Personal protective equipment (PPE) will be worn by research personnel and physical distancing will be practiced. If PPE is not available due to shortage or other issues, study procedures will be conducted virtually or marked missed as appropriate. If a potentially eligible participant is identified and known COVID positive, we will not continue enrollment procedures until 14-day quarantine is completed if asymptomatic or until asymptomatic and afebrile for 72 hours or more.

Urine collection. The urine collection cup would be dropped at their home, completed by the participant in the home and placed outside of the home. Study staff will pick-up once participant is back in the home. Additionally, study staff will ask the participant to take a picture of cup's temperature strip within 5 minutes of filling cup and email or text picture to study team.

Medication Dispensing/Administration. Medication will be picked up from the Investigational Drug Service by trained study staff. Medication will be delivered and administered to the participant by no fewer than two (2) study staff members. Medication check by virtual visit and one (1) week of medication to be delivered to the participant without direct contact. If the participant has unused medication to be returned, it will be collected at the time of delivery and managed per the Obstetrics and Gynecology Department's Medication Handling and Dispensing SOP.

D.7 Participant Management

D.7.i Criteria for dose hold and dose adjustment

In the event that side effects on the GASE are intolerable, defined as a “3” (severe) or above and, in the assessment of the investigator, related to study medication, the study clinicians will review with the participant the circumstances surrounding these side effects. Given the postpartum period is associated with changing physiology, study clinicians will discuss with the participants, perform any indicated physical or laboratory analyses and determine if these side effects are likely to be associated with study medication. If study clinicians determine based on timing, other medications, anticipated progesterone side effects and medical or social circumstances, that study medications are likely responsible for side effects, options for a dose adjustment to a lower dose or discontinuation of the medications will be reviewed with participant. Using a shared decision-making model, the participants and study clinician will determine dose reduction or discontinuation. Side effects will be assessed weekly per the study protocol until resolved or at a tolerable level (GASE <3). While the participants will have weekly check-ins regarding current symptoms and side effects, the participants will have access to study phone with a research coordinator if severe side effects were to arise in between study visits. We utilize this study phone for multiple research protocols and have successfully used this mechanism for study related activities including reports of drug side effects. If study participants report severe side effects, the PI and study clinician will be contacted immediately, triage will occur through our clinical pathway and a clinical evaluation will be scheduled as appropriate. If side effects are determined to be likely directly related to study medications, options will include decreasing dose to 100 mg twice daily (200 mg daily total), temporarily holding study medication, or permanently stopping study medication. These options will be discussed with the study participant. Study participants may continue in other study activities including study assessments and biological sample collection.

With respect to infant sedation among lactating women, given available literature on progesterone and infant sedation in the setting of breastfeeding,[5, 45, 56] we do not anticipate any sedation secondary to study drug. We will monitor closely for this and in

the event of severe sedation of infant, PI and study clinician will be notified immediately. The infant will be triaged through pediatric urgent care and review of circumstances will happen immediately to determine relationship to study drug. If infant sedation is determined to be likely directly related to study medications, options will include decreasing dose to 100 mg twice daily (200 mg daily total) or stopping study medication.

D.7 ii. Criteria for Stopping Treatment

In the event that any of scenarios below occur, treatment with micronized progesterone will stop and the participants will be retained in the study. Additional participants will be recruited to maintain the sample size.

a. Severe maternal or infant side effect (among breastfed infants) determined to be likely attributable to study medication (see Section C.7.i).
b. Systemic drug allergy, thrombosis in the postpartum period, cholestatic jaundice
c. Active suicidal ideation, or other concerns, determined to be attributable to study medication
d. Participants who become incarcerated after informed consent and screening will not be withdrawn. Study team will notify the University of Utah Institutional Review Board (IRB) if a participant becomes incarcerated during study participation. The participants will resume participation once no longer incarcerated.

D.7.ii Participants with sub-optimal participation

Sub-optimal participation in study procedure will be documented by discussion with the participant during the weekly contact and by a pill count. Participants with sub-optimal participation will be retained in the study and treatment with the randomized dose of micronized progesterone will continue. This will be used to determine drug compliance, a key feasibility outcome (Table 3). This categorization will be used to assess whether additional participants will be recruited to maintain the sample size. Missed doses are not considered to be protocol deviations. Sub-optimal participation will be defined as:

a. Participants who do not attend study visits to obtain study medication.

b. Participants who, after enrollment, report taking <80% or pills counts include <80% of tablets consumed. This proportion of participants in the total sample will only be used to determine if additional participants will be recruited to maintain overall sample size.

D.7.iii Participants who withdraw from the study

If a participant withdraws consent, we will discontinue study visits. Additional participants will be recruited to maintain the sample size.

D.8. Study Halting Criteria

The DMC will review enrollment and AEs on a regular basis, defined as once 25% (n=10), 50% (n=20) and 75% (n=30) participants have been recruited and randomized. Enrollment will not stop unless the PI is directed to stop by the DMC or the FDA. Criteria that warrant discussion of halting the study by the DMC will include more than expected occurrence of the SAEs previously known to be associated with micronized progesterone use, or SAEs unexplained by the patient's medical condition. Return to use is an expected complication in this group of participants and is associated with significant and serious maternal morbidity and mortality. Therefore, when the DMC evaluates SAEs, a distinction will be made as to whether the SAE is thought to be related to the patient's return to use, pre-existing medical conditions or whether it is thought to be related to study medication. Study halting criteria include:

Thromboembolic Events (deep vein thrombosis or pulmonary embolus)

There is a potential risk of thrombosis from progestin treatment but this risk is low. Genetic predisposition to clotting is seen in over 5% of the population and pregnancy increases the risk of thrombosis so clotting during pregnancy is uncommon but NOT an unexpected event. Doses of 400 mg of micronized progesterone have not been associated with an increased risk of clotting but the potential exists. We would expect no more than 1 cases of thrombosis (2.5%) in the 20 participants recruited to the micronized progesterone group. If the number of cases of deep vein thrombosis or pulmonary embolus in the progesterone treatment groups exceeds the number of cases in the placebo group by more 2.5% (1 cases) then these cases will reviewed by the DMC for progesterone causality. All SAEs are reported promptly to the PI and are reviewed by the DMC. The DMC should review all the thrombotic events to determine the relationship to study drug and to determine what if any action is needed.

Suicidality

There is a potential risk of exacerbation of depression with progestin treatment but this risk is low. In Yonkers et al study with similar dosing, women were not excluded if they had a mental health condition or co-occurring opioid use disorder in treatment.[5] Over 80% of women in the SUPeRAD clinic have a diagnosis of depression and anxiety. The

postpartum period is well documented to exacerbate underlying mental health conditions due to the physiological changes of the postpartum state. Additionally, postpartum women are at risk of developing postpartum depression and anxiety. Finally, women with methamphetamine use disorder are at particularly increased risk of postpartum depression and anxiety exacerbation. However, suicidality in this population remains uncommon but NOT an unexpected event. We would expect no more than 1 cases of suicidality (2.5%) in the 20 participants recruited to the micronized progesterone group. If the number of cases of active suicidality in the progesterone treatment groups exceeds the number of cases in the placebo group by more 2.5% (1 cases) then these cases will reviewed by the DMC for progesterone causality. All SAEs are reported promptly to the PI and are reviewed by the DMC. All cases of suicidality will be reviewed by the PI, immediately reviewed and reported to the DMC. The DMC will review all the active suicidality events to determine the relationship to study drug and to determine what if any action is needed.

As listed in Table 3, if EPDS or GAD7 scores increase by ≥30%, suicidal ideation or other Safety benchmarks *and* these are determined to be likely study related, the DMC will review these safety outcomes and make a recommendation for stopping the study.

E. Statistical Analysis and Sample Size Justification

E.1. Primary and Secondary Outcomes

The primary feasibility outcome is successful monthly recruitment of participants into the PROMPT study (**Table 3**).

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.[62, 63] Based on the volume of women

Table 3: Feasibility and safety outcomes

Feasibility	Benchmark
Average monthly accrual (participants/month) (primary)	1.6/month
Number of women enrolled in 24 months	40
Retention Dropout rate	< 20%
Compliance: Number of pills taken	≥ 80%
Adherence: Study session completion	≥ 80%
Safety	Benchmark
Side effects attributed to medication	< 20% positive
EPDS or GAD7 score increase ≥30%	≤ 5%
Suicidal ideation	≤ 5%
Hospitalizations	≤ 5%
Breastfeeding difficulty	≤ 30%
New pregnancy	≤ 5%
Deep vein thrombosis and/or pulmonary embolism	≤ 5%
Death	0%

seen with methamphetamine use disorder in SUPeRAD over the past three years, we anticipate seeing at least 6-8 women with MUD per month. Therefore, if we screen and recruit women across 15 months, and if 70% are eligible and interested, and of those, 70% provide informed consent; we will recruit a total of 40 women in this study who will be randomized to progesterone (n=20) versus placebo (n=20). Based on previous studies,[5] we expect 20% dropout rate (n=8) although our ability to maintain engagement in previous studies has minimized to 5–10%. To ensure retention, the study team will send study visit reminders via participants' preferred format (phone, text, email). Participants will receive gift cards for compensation per University of Utah guidelines. Participants will be compensated $100 for baseline assessment completion. At each study visit which includes biological samples (Table 3), participants will receive $50 compensation. On weeks not including biological sampling (Table 3), study participants will receive $20 compensation for completion of study assessments. At the 3-month final visit, participants will receive an additional $100 if they completed all 12 study sessions after baseline. Total compensation if all study visits are completed is $620.

Safety: We will also track safety outcomes including side effects, mental health status, breastfeeding, medical complications, and deaths. We will also track new pregnancies during the 3-month study follow-up period. Similarly, although we will track safety concerns among breastfed infants, we anticipate this risk to be quite low. Our research team will establish a DMC and will provide data to this oversight body. This board will meet when three times (at 25%, 50% and 75% recruitment points) to review summary measures for participants to ensure continued safety and data collection quality. Women with SUD are at particularly high risk of postpartum depression, anxiety, and suicidality, RAs will review the Edinburgh Postnatal Depression Scale (**EPDS**) at each study visit. If a participant scores ≥ 1 on question #10 on EPDS, which determines suicidal thoughts, the RA will follow the study participant Quick Suicide Safety Screening protocol.

Preliminary Efficacy: We will also use this study to establish preliminary efficacy by assessing return to MU and time to MU. Return to use will be defined as either self-reported MU or positive urine toxicology result. Self-reported MU will be tracked using the Substance Use Calendar (**SuCal**), which is based on the Timeline Followback and is a validated, reliable method for collection of daily information about the quantity and

frequency of all substances used.[64] The urine toxicology test is a 2-step process: first, an immunoassay for the qualitative detection of substances including amphetamines, opiate, buprenorphine, methadone, oxycodone, benzodiazepines using the E-Z Integrated Key Cup II toxicology panel; sensitivity and specificity of all substances > 95% (https://cliawaived.com/amfile/file/download/file/458/product/5440/). A confirmatory test using mass-spectrometry is reflexed to quantify amphetamines, cannabinoids, opioids (including oxycodone, methadone, or buprenorphine), benzodiazepines, and their metabolites.

F. Data Management and Quality Assurance

F.1. Investigational Product Supply

A total daily dose of 400 mg (200 mg twice daily) of oral micronized progesterone was selected to reflect currently available studies including postpartum women.[5, 45, 56] Approximately half of micronized progesterone is absorbed after oral administration with peak plasma levels with 2-3 hours and elimination half-life of 3-4 hours.[57] Oral micronized progesterone (Prometrium 100 mg; NDC 17478-0766-10 made by Akorn, Inc.; https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d9e6ec7d-85ea-41a7-88ec-88cac22d5b7d) and similar-appearing placebo capsules will be prepared by the University of Utah Investigational Pharmacy. IDS staff will over-encapsulate the active 100 mg micronized progesterone capsules using empty gelatin capsules made by Capsulin (https://capsuline.com/products/colored-gelatin-capsules-size-000-white-white-f00153-p) and hand pack with microcrystalline cellulose (https://www.letcomedical.com/avicel-ph-105-848) until fully filled. For the placebo capsules, the IDS staff will hand pack empty gelatin capsules with microcrystalline cellulose until fully filled.

F.2. Clinical Data Management

Clinical data will be acquired throughout the participant's participation in the clinical trial and will include information related to screening, randomization, enrollment, outcome, adherence, and adverse outcomes. These data will be collected on case report forms (CRFs) specific to this study.

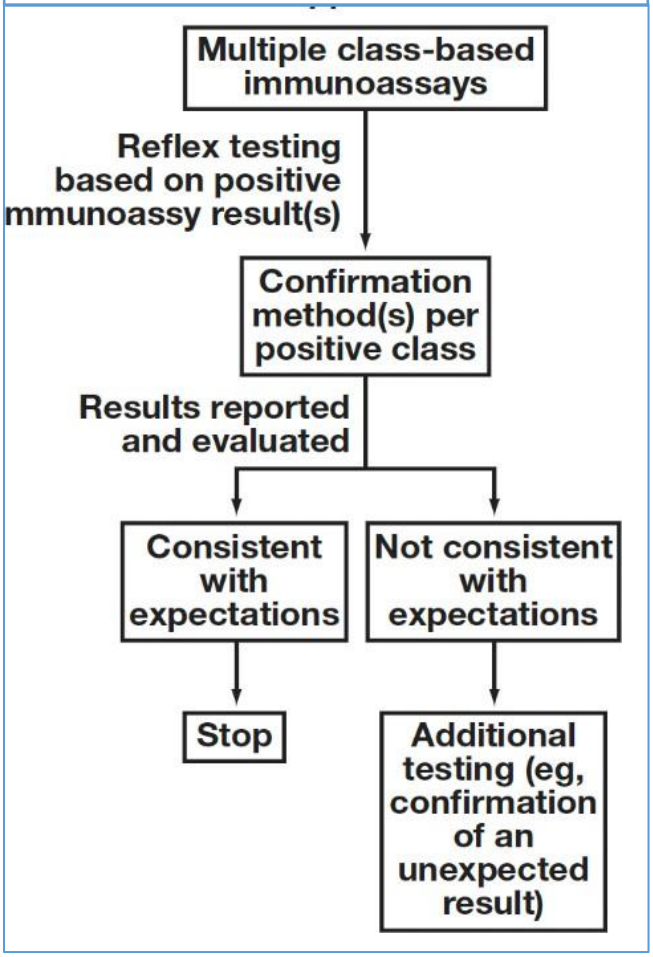
All key data from CRFs will be entered into the University of Utah's REDCap database program, which will be used as a secure web application for research data storage and archiving. The password protected database provides system validation, metadata, and is supported by University of Utah's Center for Clinical Translational Sciences servers. The database provides features including auto-validation, calculated fields, branching/skip logic, and data quality tools such as Data Resolution Workflow which tracks query generation, data alterations, and resolution.

F.3. Laboratory Test Results

The Center for Human Toxicology will perform the salivary samples allopregnanolone levels. Under the direction of Dr. Diana Wilkins, saliva samples will be processed using a highly sensitive enzyme immunoassay for allopregnanolone levels validated for both serum and salivary samples (AssayPro, St. Charles, MO). Normal human levels of allopregnanolone range from 414.04–1051.02 pg/ml. Per the test manufacturer, the minimum detectable dose of allopregnanolone as calculated by 2 standard deviations from the mean of a zero standard is 0.28 pg/ml, with an average intra-assay coefficient of variation of 5.5%, and an inter-assay coefficient of variation of 10.2%. We will process each sample twice and batch process the saliva samples every other month to avoid stability issues for stored saliva samples and kit expiration dates. We estimate that 15% of samples will need triplicate analysis due to: a) initial two sample difference of >10%, b) failed batch quality control, or c) need for dilution to obtain accurate quantity.

All urine drug tests will be performed in a Clinical Laboratory Improvement Amendments accredited clinic laboratory (ARUP Laboratories, Salt Lake City, UT). All equipment to perform urine toxicology per the ARUP protocol (**Figure 5).**

Figure 5 Schematic illustration of ARUP approach to drug testing. LC-TOF/MS, liquid chromatography time-of-flight mass spectrometry. Adapted from McMillin, G. A., Marin, S. J., Johnson-Davis, K. L., Lawlor, B. G., & Strathmann, F. G. (2015). A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. *American journal of clinical pathology*, *143*(2), 234-240.



- Urine drug screens will be performed with 11 HEIA reagent kits following the manufacturer's instruction and the AU400 analyzer (Beckman Coulter, Brea, CA).
- Syva Emit II Plus reagents (Siemens, Tarrytown, NY) will be used for the following drug classes (cutoff concentration in ng/mL):
    - Amphetamines (300)
    - Barbiturates (200)
    - Benzodiazepines (200)
    - Cannabinoids (20)
    - Cocaine (150)
    - Methadone (150)
    - 3,4-methylenedioxy-*N*-methylamphetamine (MDMA, ecstasy, 500)
    - Opiates (300)
    - Phencyclidine (PCP, 25)
    - Propoxyphene (300)
- DRI Oxycodone Assay reagents from Microgenics (Fremont, CA)
    - Oxycodone testing (100-ng/mL cutoff)

Urine samples that test positive for any immunoassay will be reflexed to a corresponding quantitative confirmation test, wherein identification of a compound(s) responsible for the positive immunoassay result was based on targeted, mass spectrometric detection. They will be prepared using solid-phase extraction, and deuterated internal standards were added. Barbiturate and cocaine metabolite tests are performed by gas chromatography

coupled to mass spectrometric detection (Agilent 6890N/5973; Agilent Technologies, Santa Clara, CA), subsequent to preanalytical derivatization reactions. Tests performed by liquid chromatography are coupled to tandem mass spectrometry (Waters Acquity/TQD [Waters, Milford, MA] or Agilent 1260 [Agilent Technologies]/AB Sciex 5500 [AB Sciex, Framingham, detection. Microgenics (Fremont, CA). Cross-reactivity profiles for these assays MA]) include amphetamines (including MDMA), benzodiazepines, THCA (a common cannabinoid metabolite), methadone, opiates (including oxycodone), PCP, and propoxyphene. Preanalytical hydrolysis reactions to liberate glucuronide conjugates will be incorporated in THCA and benzodiazepine assays.

These laboratory results will be sent to the PI and merged with the data for this study. All data from CRFs and biological analysis will be linked using a participant identification number assigned at study entry.

G. Appendix A - SUPeRAD Clinical and Research Staff Qualifications

Marcela C. Smid MD MA MS is Assistant Professor at the University of Utah Department of Obstetrics and Gynecology and Adjunct faculty in the Departments of Psychiatry and Psychology. She is core research faculty in the University of Utah's Division of Epidemiology PARCKA. She a dual boarded maternal fetal medicine specialist (American Board of Obstetricians and Gynecologists) and addiction medicine (American Board of Preventative Medicine). She is medical director of the Substance Use and Pregnancy – Recovery, Addiction, Dependence (SUPeRAD) clinic. Her research and clinical interests include perinatal substance use disorder, maternal mortality and maternal mental health. She was an NIH K12 Women's Reproductive Health Research Scholar (2018-2020) and is over 50% funded by several research projects including CDC funded MAT-LINK (https://www.cdc.gov/ncbddd/aboutus/mat-link.html) , 1) Optimizing Pregnancy Treatment Interventions for Moms (PI Cochran; CDC R01CE002996) and 2) Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs): A Pragmatic Randomized Trial Comparing Two Buprenorphine Formulations (CTN80; Site PI Cochran; NIDA UG1DA049444) among others. She has extensive experience with OGRN and PARCKA coordinating and assessing pregnant women with opioid use

disorder for enrollment, recruitment and retention in clinical trials, including medication trials. Dr. Smid will be available to Ms. Humiston to provide mental and physical health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study. Dr. Smid has completed the online C-SSRS research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Jasmin E Charles, PA-C is a certified Physician Assistant and the Clinical Director of SUPeRAD clinic since its founding in 2017. She received her undergraduate degree from Utah State University and attended the PA program at the University of Utah. She is a member of the Utah Association of Physician Assistants and American Academy of Physician Assistants. Her areas of clinical interest and expertise include all aspects of women's healthcare with particular interest in substance use and maternal mental health. She has extensive experience and expertise in assessing and triaging physical and mental health concerns of pregnant and postpartum women. She is a study clinician on multiple studies including the NIDA funded MOMs trial and has worked closely with the OGRN and PARCKA teams. Ms. Charles will be available to Ms. Humiston to provide mental and physical health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study. Ms. Charles has completed the online C-SSRS research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Elizabeth Howell, MD, MS, is Associate Professor of Psychiatry (Clinical) at the University of Utah School of Medicine in Salt Lake City, Utah, with an inpatient and outpatient practice at the Huntsman Mental Health Institute. She is the Training Director for the Addiction Psychiatry and Addiction Medicine fellowship programs at the University of Utah School of Medicine. Dr. Howell is Board-certified in Psychiatry and Addiction Psychiatry by the American Board of Psychiatry and Neurology, and in Addiction Medicine by the American Board of Preventive Medicine. She is currently accepting inpatients at the Huntsman Mental Health Institute and accepts

consultation referrals from other physicians. She works closely with Dr. Smid clinically and is available for immediate consultation for any patient in SUPeRAD or involved in a research protocol. Dr. Howell will be available to Ms. Humiston (lead clinical research coordinator, see below) to provide psychiatric triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

Program for Addiction Research, Clinical Care, Knowledge, and Advocacy (PARCKA) Staff that Support SUPeRAD Research Activities

The primary responsibility for patient research assessment and long term research monitoring and engagement will be provided the PARCKA staff. These staff will work closely with the clinical staff at the SUPERAD clinical to ensure participant health and safety during the conduct of this study.

Jerry Cochran PhD MSW is an Associate Professor in the Department of Internal Medicine, Division of Epidemiology at the University of Utah and serve as the Director of Research for the newly established Program on Addiction Research, Clinical Care, Knowledge, and Advocacy within the Division of Epidemiology. He is also adjunct Associate Professor appointment with the University of Utah School of Medicine, Department of Psychiatry. He has extensive expertise in system- and clinical-level behavioral health services research. My experience has focused on development and testing of evidence-based practices for addressing opioid misuse, use disorder, and related health conditions and outcomes, with the majority of funding for this work from the National Institute on Drug Abuse and Centers for Disease Control and Prevention. I am a Multiple-PI for the Greater Intermountain Node of the NIDA Clinical Trials Network (CTN), in which I lead, am site PI, and coinvestigator on large scale multisite studies testing interventions for the opioid epidemic. Currently, he is a PI and Site Multiple PI on 2 clinical studies testing a interventions for women with opioid use disorder: 1) Optimizing Pregnancy Treatment Interventions for Moms (PI Cochran; CDC R01CE002996) and 2) Medication Treatment for Opioid Use Disorder in Expectant Mothers (MOMs): A Pragmatic Randomized Trial Comparing Two Buprenorphine Formulations (CTN80; Site PI Cochran; NIDA UG1DA049444. He works closely with the SUPeRAD clinic, which is

the main recruitment site for these trials. He and Dr. Smid work closely to ensure the safety of all patients enrolled in clinical trials at this site.

Adam Gordon MD is a tenured Professor of Medicine and Psychiatry at the University of Utah School of Medicine and is Core Faculty member of the VA Salt Lake City Informatics, Decision- Enhancement and Analytic Sciences (IDEAS) Center, a Department of Veterans Affairs Health Services Research and Development HSRD Centers of Innovation (COIN). He is the Director of the Program for Addiction Research, Clinical Care, Knowledge, and Advocacy (PARCKA); an MPI of the Greater Intermountain Node (GIN), a node of the NIH NIDA Clinical Trials Network Node; and direct several national initiatives to improve the access and quality of care among patients with opioid misuse in the Veterans Health Administration. He is well versed in research protocols and is available for both clinical and research consultation in the event of safety concerns for a research participant.

Gina Gregovich, Clinical Research Manager, is a full-time employee with PARCKA. Gina has a bachelor's degree from the University of Utah and maintained a Certified Clinical Research Professional (CCRP) credential from 1998 to 2013. In 2013, Gina transitioned from clinical trials to medical device manufacturing, expanding her regulatory knowledge to quality management systems (21 CFR 820, 21 CFR 211, ISO 13485). Shifting back to clinical trials in 2019, Gina will be eligible to re-certify as a CCRP in 2022 through the Society of Clinical Research Associates (SoCRA). Gina previously served a three-year term on the SoCRA board of directors. Gina has over 20 years' experience working in clinical trials, phase I to IV, single-site to multicenter, investigator-initiated, industry-sponsored and NIH (NCI and NIDA) sponsored clinical trials. Gina established the research compliance office (RCO) at Huntsman Cancer Institute, providing oversight on investigator-initiated clinical trials and providing administrative support for the data and safety monitoring board (DSMB). Gina has served as a volunteer auditor for National Cancer Institute (NCI), cooperative group (NCTN) program. Gina currently serves as the Greater Intermountain Node (GIN) coordinator serving in a leadership role on Clinical Trials Network (CTN) studies at our site.

Kristi Carlston received her bachelor's degree in Health Promotion and Education from the University of Utah and is certified as a clinical research coordinator (CCRC) through the Association of Clinical Research Professionals. Kristi is a senior research coordinator with the University of Utah, is a full time employee, and has ten years of progressive research experience that includes design, implementation and management of clinical research projects in an academic setting with vulnerable populations. Kristi is responsible for coordination support to study investigators, staff supervision and data management on several multi-site projects. She will assist Ms. Humiston on the study in terms of carrying out patient assessments (including DSM V checklist, EPDS, GAD7, C-SSRS), consenting, ensuring intervention adherence, and notifying clinical staff should any physical health or behavioral needs arise for patients. Ms. Carlston has completed the online C-SSRS research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Grace Humiston, Clinical Research Coordinator, is a full time employee of the University of Utah in the Department of Epidemiology. Grace has a Bachelor of Science in Gender Studies with a minor in Pediatric Clinical Research from the University of Utah. She is currently enrolled in the University of Utah's MBA program, anticipated graduation Fall 2022. Grace has coordinated multiple trials in the University of Utah Department of Psychology studying cardiovascular responses to in-lab stressors as well as sleep quality as a risk for suicidality, specifically in veterans. Prior to joining PARCKA, Grace was coordinating phase I-III interventional clinical trials in oncology at Huntsman Cancer Institute, most of which had IND applications. Grace is a trained and practicing birth doula and has been attending births for the past 8 years. She has completed the Harm Reduction Navigator and HIV/HCV Prevention Counseling trainings through the Utah Department of Health and has worked extensively with high-risk patients through Utah AIDS Foundation, Planned Parenthood of Utah, and Utah Harm Reduction Coalition. She will be the lead research coordinator on the study in terms of carrying out patient assessments (including DSM V checklist, EPDS, GAD7, C-SSRS), consenting, ensuring intervention adherence, and notifying clinical staff should any physical health or behavioral needs arise for patients. Ms. Humiston has completed the online C-SSRS

research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Stephanie Castro is a full-time Research Coordinator at PARCKA. She has a Masters in Public Health. Prior to serving as the lead Research Coordinator for the PROMPT trial, she served as the lead coordinator for the NICHD funded Child and Family Study which recruited primarily from the SUPeRAD clinic. This was an observational cohort study of maternal-infant dyads affected by opioid use disorder. She has extensively experience in working with this population. She will be responsible for the recruitment and retention of study participants. Given her experience in research projects with this population, Ms. Castro has extensive experience with assessing for safety among both women and their infants. Ms. Castro has completed the online C-SSRS research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Elysha Cash is a full-time Research Assistant at PARCKA. She has extensively experience in working with this population and also recruits for the NNIDA CTN funded MOMS trial. She will be responsible for the recruitment and retention of study participants and assisting Stephanie Castro. Ms. Cash has completed the online C-SSRS research training module (https://cssrs.columbia.edu/training/training-research-setting/) prior to the initiation of this study.

Mitchell Garets is a full time Research Analyst at PARCKA. Mitchell holds both a bachelor and master's degree in Social Work from the University of Utah. Mitchell is trained in Enhanced Motivational Interviewing, Substance Use Disorder Treatment, and Anti-Discrimination Response. Mitchell also holds certification in Leadership, Justice, and Community Practice from the University of Utah's College of Social Work. Mitchell has several years' experience working in substance use disorder research and treatment. He has offered research support and/or coordination on several local and national funded multi-site studies, and has direct experience offering clinical and case management services to pregnant individuals with substance use disorders.

Ashley White works as a full time as a Social Service Worker for the Program for Addiction Research, Clinical Care, Knowledge and Advocacy. She is a licensed Clinical Mental Health Counselor in Utah, with a background and training in substance use treatment. She has extensive human services experience, including as a psychotherapist and in the field of psychological research. In addition to her role at PARCKA, she has also worked as a research assistant in two Cognition labs out of Colorado State University. She earned a Bachelor of Science in Psychology from Colorado State University, and a Master of Arts in Transpersonal Counseling Psychology from Naropa University. She has trained in the modality of Motivational Interviewing, various mindfulness-based therapies and trauma-informed care. She will be available to Ms. Humiston to provide mental health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

Obstetrics and Gynecology Research Network (OGRN) Staff that Support SUPeRAD Research Activities

Torri Metz, MD, MS, is an Associate Professor of Obstetrics and Gynecology, a Maternal-Fetal Medicine sub-specialist and Vice Chair of Research of Obstetrics and Gynecology. Dr. Metz's interested in the impact of marijuana use in pregnancy on the mother and newborn, maternal congenital heart disease, and factors influencing mode of delivery. Dr. Metz will be available to OGRN and PARCKA research coordinators to provide mental and physical health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

Kathy Harvey is the Associate Director of Research and Science. She has a BA in Biology from Utah State University and has worked in the Obstetrics and Gynecology Department at the University of Utah for over 17 years. During that time, she had had comprehensive experience with all aspects of research, from clinical screening and enrollment, to laboratory and biospecimen management, to high-level research administration duties. She has extensive opportunities to lead and facilitate protocols

involving maternal substance use disorder, as well as maternal mental health during pregnancy and postpartum. As the leader of a robust research administration team, she supervises and ensures the successful management of all protocols we acquire.

Elizabeth Turner and Valerie Joseph are the OBGYN Research Compliance Managers who manages human subjects protection issues for all OBGYN research studies. This includes IRB submissions from initial submission through study close-out, FDA documentation for IND/IDE investigator initiated studies, FDA inspections/audits and compliance oversight.

Additional SUPeRAD Clinicians available for study protocols

Michelle Debbink, MD PhD is a maternal fetal medicine specialist and board certified OB/GYN (American Board of Obstetricians and Gynecologists). Dr. Debbink received her bachelor's degrees in Sociology and Health Policy from Rice University in Houston, Texas. She received her medical degree from the University of Michigan Medical School and completed her PhD in Health Services Organization and Policy at the University of Michigan School of Public Health. Her research focus in on health disparities. She is well versed in assessing and triaging pregnant and postpartum women with mental health and substance use disorders, including those in SUPeRAD affiliated research protocols. Dr. Debbink will be available to Ms. Humiston to provide mental and physical health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

Aurelia R. Wann, DNP, WHNP-BC is a Women's Health Nurse Practitioner at University of Utah Health. She is board certified and received her Doctorate in Women's Health Nursing Practice from the University of Utah. Aurelia has 16 years of experience in women and newborn healthcare. Part of this experience has included assisting with the design and creation of the Special Care Nursery at LDS Hospital. Her passion for women's healthcare crosses the lifespan from tending to individuals during pregnancy or menopause. She taught the Neonatal Resuscitation

Program for Intermountain Healthcare for eight years and shoulder dystocia simulation for labor and delivery for three years. Professional memberships include Nurse Practitioners in Women's Health, Utah Nurse Practitioners, and the Association of Reproductive Healthcare Professionals. Ms. Wann will be available to Ms. Humiston to provide mental and physical health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

Julia Ewansowski, LCSW MPH is a maternal fetal medicine social worker. She works within the Division of Maternal Fetal Medicine and works closely with pregnant and postpartum women. She providers support to all MFM clinic and works closely with the certified social worker embedded within the SUPeRAD clinic to respond to emotional concern or situations. Ms. Ewansowski will be available to Ms. Humiston to provide mental health triage, assessment, referral, and follow up should patients have a need arise during the conduct of the study.

H. **Appendix B SUPeRAD Clinic Community partners**

House of Hope	**House of Hope** is a private, non-profit organization offering residential, day treatment, and outpatient substance use disorders treatment for adult women. Services are offered at seven facilities located in Salt Lake City and Provo, Utah. Services include therapeutic day treatment services for children while their mothers attend treatment and an aftercare program to help provide a safe place for women to continue growing in their recovery process. ***The Nesting Place*** is a planned facility for pregnant women and new mothers to start their recovery journey while cultivating healthy and strong relationships with their newborns.
Odyssey House	**Odyssey House** services include 1) psychiatrically oriented treatment for mothers with Substance Use Disorder including psychiatric, psychological, medical, educational, vocational, and recreational services, 2) alternative school provides individualized education, remediation, and high school graduation preparation through ***Horizonte School,*** *3)* ***W*****omen and Children's Program** for single mothers with children under age 9, 4) outpatient and intensive outpatient programs, 5) Transitional Housing Aftercare Program to private apartments for post-inpatient clients and relapse prevention and aftercare groups, 6) prevention programs for high risk youths/adults, and 7) day treatment for children 0-9 years whose mothers are in treatment at Odyssey House.
USARA Utah Support Advocates for Recovery Awareness	**Utah Support Advocates for Recovery Awareness (USARA)**'s mission is to celebrate, advocate, support, and empower people in all stages of addiction recovery through connecting to resources, building community, and raising awareness that long term recovery is possible. Recovery Support Services are provided by people who share their lived-experience of addiction and recovery and offer clients a network for building strong and mutually supportive relationships with informal supports and formal systems in their communities.
PROJECT REALITY Making Recovery a Reality Substance Abuse Treatment and Prevention Services	**Project Reality** serves adults with opioid use disorder who seek lifelong recovery and wellness. Our services include 1) Medication Assisted Treatment with buprenorphine-based products, methadone, and long-acting naltrexone, 2) psychotherapy, 3) individual, group, and family psychotherapy and counseling, 4) physical health assessments with attention to primary care needs, psychiatric assessments, and smoking cessation, 5) drug screening, medication dispensing and observed daily dosing, 6) infectious disease education, testing and counseling (Hepatitis, TB, STD), 7) case management , and 8) parenting classes.

	**BAART Salt Lake City**, formerly known as Metamorphosis, offers evidence-based medication-assisted treatment for Opioid Use Disorder along with counseling, case management, and community resource referrals for patients struggling with addiction. Experienced clinical professionals at BAART provide every patient with individualized addiction treatment in a judgment-free atmosphere. Whether the patient is misusing prescription opioids or illicit opioids, the medication-assisted treatment is prescribed and managed under the supervision of a licensed medical provider.
	**New Season Bountiful Treatment Center** provides opioid addiction treatment and recovery services to Salt Lake City and surrounding areas including Centerville, Farmington, Kaysville, Taylorsville, Murray, Millcreek, Woodridge Terrace, West Valley City and West Jordan. We provide outpatient services including methadone treatment, individual, group and family counseling, medical exams and referrals as needed.
	**Tranquility Place** offers a wide range of patient services **including** individual counseling, medical dosing evaluation, random urine analysis, tuberculosis testing, bloodwork analysis, group counseling, and initial physicals. Our goal at Tranquility Place is to treat patients with compassion, dignity, and respect in each phase of recovery. Throughout treatment, you will work closely with a substance abuse counselor to develop a treatment plan that meets your needs with the goal of improving your quality of life and overcoming opioid dependency and maladaptive behaviors.

J. Appendix C Excluded Medications

- Barbiturates
  - Benzylbutylbarbiturate
  - Butalbital
  - Amobarbital
  - Pentobarbital
  - Secobarbital
  - Sodium thiopental
  - Phenobarbital
- Benzodiazepines
  - Clonazepam
  - Diazepam
  - Estazolam
  - Flunitrazepam
  - Lorazepam
  - Midazolam
  - Nitrazepam
  - Oxazepam
  - Triazolam
  - Temazepam
  - Chlordiazepoxide
  - Alprazolam
  - Clobazam
  - Clorazepate
  - Etizolam
- Nonbenzodiazepine hypnotics
  - Eszopiclone
  - Zaleplon
  - Zolpidem
  - Zopiclone
- Orexin antagonists
  - Suvorexant
- First generation Antihistamines
  - Diphenhydramine
  - Dimenhydrinate
  - Doxylamine
  - Promethazine
  - Brompheniramine
  - Chlorpheniramine
  - Hydroxyzine
- Herbal sedatives
  - Duboisia hopwoodii
  - Prostanthera striatiflora
  - Catnip
  - Kava (Piper methysticum)
  - Valerian

    - Products with tetrahydrocannabinol (THC)
    - Passiflora spp.(passiflora incarnata)
    - Physochlaina - notably P. infundibularis
    - Validol
- Methaqualone and analogues
    - Afloqualone
    - Cloroqualone
    - Diproqualone
    - Etaqualone
    - Methaqualone
    - Methylmethaqualone
    - Mebroqualone
    - Mecloqualone
    - Nitromethaqualone
- Monoamine oxidase inhibitors (MAOI) anti-depressants
    - isocarboxazid
    - phenelzine
    - tranylcypromine
    - selegiline
- Skeletal Muscle Relaxant
    - Meprobamate
    - Baclofen
    - Carisoprodol
    - Cyclobenzaprine
    - Metaxalone
    - Methocarbamol
    - Tizanidine
    - Chlorzoxazone
    - Orphenadrine
    - Gabapentin
    - Pregabalin
- Opioids
    - Tramadol
    - Tapentadol
    - Morphine
    - Diamorphine
    - Hydromorphone
    - Oxymorphone
    - Oxycodone
    - Hydrocodone
    - Propoxyphene
    - Meperidine
    - Fentanyl
    - Codeine
    - Carfentanil
    - Remifentanil
    - Alfentanil
    - Sufentanil

    - Opium
- Certain Antidepressants including:
    - Amitriptyline
    - Trazodone
    - Mirtazapine
    - Doxepin
    - Desipramine
    - Imipramine
    - Clomipramine
    - Amoxapine
    - Trimipramine
    - Nortriptyline
    - Nefazodone
- Antipsychotics
    - Olanzapine
    - Clozapine
    - Thiothixene
    - Haloperidol
    - Fluphenazine
    - Prochlorperazine
    - Trifluoperazine
    - Loxapine
    - Quetiapine
    - Asenapine
- Other
    - Dextromethorphan
- Stimulants
    - Amphertamine
    - Dextroamphetamine
    - Lisdexamfetamine dimesylate
    - Methylphenidate
    - Dexmethylphenidate
    - Metadate ER
    - Methylin ER

Bristol Breastfeeding Assessment Tool

	0 **Poor**	1 **Moderate**	2 **Good**	**Score**
POSITION ING				
Baby well supported; Tucked against mother's body; Lying on side /neck not twisted; Nose to nipple; Mother confident handling baby	No or few elements achieved **Needs to be talked through positioning**	Achieving some elements **Some positioning advice still needed**	Achieving all elements **No positioning advice needed**	
ATTACHMENT				
Positive rooting; Wide open mouth; Baby achieving quick latch with a good amount of breast tissue in mouth; Baby stays attached with a good latch throughout feed	Baby unable to latch onto breast or achieves poor latch. No/few elements achieved **Needs to be talked through attachment**	Achieving some elements **Some advice on attachment needed**	Achieving all elements **No advice on attachment needed**	
SUCKING				
Able to establish effective sucking pattern on both breasts (initial rapid sucks then slower sucks with pauses). Baby ends feed.	No effective sucking; no sucking pattern	Some effective sucking; no satisfactory sucking pattern; on and off the breast	Effective sucking pattern achieved	
SWALLOWING				
Audible, regular soft swallowing- no clicking	No swallowing heard; clicking noises	Occasional swallowing heard; some swallows noisy or clicking	Regular, audible, quiet swallowing	

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