PROTOCOL TITLE:
Morphine versus Methadone for Opiate Exposed Infants with Neonatal Withdrawal Syndrome: A pilot study

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER:

Version 5.0

DATE:

4/9/18

REGULATORY FRAMEWORK:

Please indicate all that apply:

	DOD (Department of Defense)
	DOE (Department of Energy)
	DOJ (Department of Justice)
	ED (Department of Education)
	EPA (Environmental Protection Agency)
	FDA (Food and Drug Administration)
	HHS (Department of Health and Human Services)
	Other:

Is this a clinical trial under ICH-GCP E6? Yes No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. Yes No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

1.1. Describe the purpose, specific aims, or objectives.

1.2. State the hypotheses to be tested.

We propose a pilot randomized controlled trial to evaluate morphine vs methadone treatment of infants with in-utero opiate exposure. Specifically, length of treatment, need for additional medication to treat withdrawal, and length of hospital stay will be compared.

2. Background

2.1. Describe the relevant prior experience and gaps in current knowledge.

2.2. Describe any relevant preliminary data.

2.3. Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Over the last ten years there has been a striking increase in opiate abuse in pregnant women, and the optimal care for neonatal abstinence syndrome is now an important public health issue. Neonates exposed to opiates in utero can develop a constellation of withdrawal symptoms known as neonatal abstinence syndrome (NAS) that includes CNS irritability, gastrointestinal side effects and autonomic dysfunction[1]. Infants with NAS are at risk for multiple medical complications including failure to thrive and seizures, they often require prolonged hospital stays and account for significant health care costs. From 2009 to 2012 the incidence of NAS increased from 3.4 to 5.8 per 1000 hospital births, for a total of 21 732 affected infants[2]. The average length of stay for infants with NAS is 16.9 days, and admissions for NAS account for an estimated $1.5 billion in hospital charges[2].

Between 21% to 94% of exposed infants develop signs of withdrawal severe enough to warrant pharmacologic treatment[1,5,6]. Investigators have recently shown that stringent weaning protocols decrease neonatal opiate exposure and length of hospital stay[3,7]. Multiple protocols for opiate weans exist, including methadone, morphine, and now buprenorphine, however evidence surrounding the optimal treatment regimen is conflicting. While one study comparing methadone to morphine for infants with NAS demonstrated no significant difference in length of hospital stay,[3] others have found decreased length of stay with methadone[4]. These studies have used different weaning protocols and have not calculated morphine equivalents between study arms, making direct comparisons between morphine and methadone difficult.

Methadone has been the standard of care for opioid abuse treatment in pregnancy since the 1970s. At University of New Mexico, infants exposed to opiates including methadone or heroin in-utero who develop NAS requiring pharmacologic treatment undergo a treatment wean with methadone, whereas infants exposed to buprenorphine undergo a wean with morphine. However, morphine is used frequently to treat neonatal abstinence syndrome among methadone-exposed infants throughout the US. Anecdotal evidence at our institution suggests that infants treated with morphine have shorter hospital stays compared to infants treated with methadone.

References

1. Hudak ML, Tan RC; COMMITTEE ON DRUGS; COMMITTEE ON FETUS AND NEWBORN; American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics. 2012 Feb;129(2):e540-60. doi: 10.1542/peds.2011-3212. Epub 2012 Jan 30.

2. Patrick SW, Davis M M , Lehmann C U and Cooper W O Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012 *Journal of Perinatology* (2015) 35, 650–655; doi:10.1038/jp.2015.36; published online 30 April 2015

3. Hall ES, Wexelblatt SL, Crowley M, et al; OCHNAS Consortium. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. Pediatrics. 2014;134(2). Available at: www.pediatrics.org/cgi/ content/full/134/2/e527

4. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol* 2015; 35(4): 278–283

5. Ebner N., Rohrmeister K., Winklbaur B., et al: Management of neonatal abstinence syndrome in neonates born to opioid maintained women. Drug Alcohol Depend 2007; 87: pp. 131-138

6. Logan B.A., Brown M.S., and Hayes M.J.: Neonatal abstinence syndrome: treatment and pediatric outcomes. Clin Obstet Gynaecol 2013; 56: pp. 186-192

7. Hall ES, Wexelblatt SL, Crowley M, Grow JL, Jasin LR, Klebanoff MA, McClead RE, Meinzen-Derr J, Mohan VK, Stein H, Walsh MC; OCHNAS Consortium. Implementation of a Neonatal Abstinence Syndrome Weaning Protocol: A Multicenter Cohort Study. Pediatrics. 2015 Oct;136(4):e803-10. doi: 10.1542/peds.2015-1141. Epub 2015 Sep 14.

3. Study Design

3.1. Describe the study design (e.g., observational; randomized placebo-controlled clinical trial, etc.)

This study is a pilot randomized controlled clinical trial of morphine versus methadone for the treatment of neonatal withdrawal syndrome for neonates exposed to opiates other than buprenorphine in utero.

3.2. Describe blinding, if applicable

Since we are using existing treatment protocols that include different timing intervals of medication administration between methadone and morphine, neither nursing staff nor physicians can be blinded.

4. Inclusion and Exclusion Criteria

4.1. Describe how individuals will be screened for eligibility

Initial screening will include all infants with in –utero exposure to opiates other than buprenorphine, including methadone, heroin, and prescription opiates. In utero-exposure will be determined by self-reported opiate use in pregnancy and urine drug screen positive for opiates and/or methadone on admission to the hospital.

4.2. Describe the criteria that define who will be included or excluded in your final study sample.

Infants will be eligible if they are born at UNM Hospital at greater than 34 weeks gestation, and if their primary in-utero drug exposure was and opiate other than buprenorphine, as evidenced by maternal history and a maternal or infant urine drug screen positive for methadone and/or opiates on admission. Infants will be excluded if they are born prior to 34 weeks, require neonatal intensive care unit stay greater than 24 hours, have any serious medical comorbidities, and if the primary substance exposure in-utero was buprenorphine, or was not opiates.

4.3. Indicate specifically whether you will include each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Our study population is newborns only.

1.4. Indicate if you excluding any particular populations (e.g., women, children, persons not fluent in English, a particular racial or ethnic group, etc.) and provide justification

We will exclude infants whose consenting parent or guardian is not fluent in English or Spanish. Based on our current Milagro clinic population, non-English speaking families are extremely rare. We will include a Spanish short-consent form in the case of unanticipated Spanish speaking families.

2. Number of Subjects

2.4. If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

N/a

2.5. Indicate the number of subjects to be recruited at this site.

100 infants. This estimate is based on historical review of the number of infants exposed to methadone or heroin in utero delivered at UNM per year. We are increasing the recruitment goal to 100 after finding our overall birth rate is lower and the infant withdrawal rate is lower than expected due to changes in hospital policies since the withdrawal rate was last calculated (i.e. rooming-in). The recruitment will take place over 2 years.

2.6. Provide sample size justification

Note 1: When studies involve consent, an individual is considered a research subject once they have provided consent. If the research includes screening procedures after consent, please indicate the number of subjects that need to be recruited and the number that will actually participate in the research post-screening.

Note 2: When studies involve the use of human data or specimens, the number should describe the total number of individuals from whom those data or specimens originated.

Note 3: Over-enrollment (exceeding the numbers described to the IRB) is a protocol violation. If you need to include more subjects, a modification must be submitted to and approved by the IRB prior to doing so.

This pilot study will provide estimates of effect size, and standard deviations for sample size calculations for a larger RCT.

Using data gathered from births on the Family Maternal Child Health service in 2015, we estimate approximately 78 newborns with in-utero methadone or heroin exposure per year. To find a difference of 3 days in length of hospital stay, 272 infants would need to be recruited, which we predict would take over 3 years. We have found however that our birth rate is lower than expected and the infant withdrawal rate is also lower than expected. For this reason, an initial pilot study will be conducted with infants born over 2 years from approval of the IRB (approximately September 2016- September 2018, 100 infants). This initial pilot study will enable data to be gathered regarding feasibility and troubleshooting of the study protocol in preparation for a larger study.

3. Study Timelines

3.4. Describe:

- *The duration of an individual subject's participation in the research*
- *The duration anticipated to enroll all subjects*
- *The expected duration for the investigators to complete the study (complete analysis)*

Parents or guardians of eligible infants will be approached for enrollment and randomization within 12 hours of birth. Infants will participate until hospital discharge. Based on our projected numbers of eligible infants over 1 year, enrollment time for a pilot study would be approximately 1 year, with an additional 6 months for data analysis.

Study Endpoints

3.5. Describe the primary and secondary study endpoints.

3.6. Describe any primary or secondary safety endpoints.

3.7. Describe any exploratory endpoints.

The primary research endpoint is length of hospital stay. Secondary research endpoints include length of treatment, need for a second treatment agent, need for assisted nutritional support (including increased kcal requirement, procedures including NG tube placement), need for additional consults outside the range of traditional complications of NAS, parent satisfaction, breastfeeding initiation, breastfeeding status at discharge.

There are no safety endpoints because the morphine protocol is already in use for buprenorphine exposed babies at UNMH and has been proven for safety.

4. Research Setting

4.4. Describe the sites or locations where your research team will conduct the research.

Participants will be recruited from UNMH during inpatient hospitalization when presenting for birth and from Milagro prenatal clinic in the third trimester. Participants will primarily be pooled from births to the patients of the Milagro prenatal substance abuse program, which has locations currently at the Family Medicine Center, the Southeast Heights Clinic, and the Addiction and Substance Abuse Program.

4.5. Identify where your research team will identify and recruit potential subjects.

The research team will recruit patients prenatally at the above clinic locations in the third trimester of pregnancy, and/or within 24 hours of birth on Labor and Delivery, the Mother Baby Unit, and the Intermediate Care Nursery-3. If parents or guardians are interested in participating, the infant's care provider will ask permission to inform the study staff to approach them about participating in the study. IRB-approved study staff will approach only those parents or guardians who give permission to their infant's care providers. The study team will approach potential participants in person in the hospital, or on the phone after the potential participant's provider has presented the study to the parents or guardians and after they have indicated willingness to further discuss the study with a research team member. A research assistant will maintain personal contact with all parents or guardians and a 24-hour number to reach study personnel with any concerns will be available.

4.6. Identify where research procedures will be performed including any laboratory analytics

Maternal and or infant urine drug screens used to determine study eligibility will be performed at UNM inpatient laboratory as part of the standard newborn hospitalization protocol.

4.7. Describe the composition and involvement of any community advisory board

N/a

4.8. For research conducted outside of UNM HSC and its affiliates describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure/requirements (Note: include any approvals (IRB, facility, or other) with your submission)*

n/a

9. Resources Available

9.1. Describe the qualifications of the PI and study staff (e.g., training, experience, oversight) as required to perform the research. When applicable describe their knowledge of the local study sites, culture, and society.

Nicole Yonke, MD, MPH (Principle Investigator) is an Assistant Professor/ Attending Physician in Family Medicine at UNM. She attended medical school and completed her Family Medicine and Preventive Medicine residencies at Oregon Health Sciences University. She completed her

fellowship in Maternal Child Health and joined faculty at UNM in 2013. Her special interests include women's health, caring for pregnant women and newborns, women affected by substance abuse during pregnancy, family planning, and preventive medicine.

Mary Beth Sutter, MD is an Associate Professor/ Attending Physician in the Department of Family Medicine. She completed her residency in Family Medicine at Memorial Hospital in Pawtucket, Rhode Island and completed her fellowship in Maternal Child Health at the University of New Mexico in 2015. Clinically she works with the Maternal Child Health Team, as well as attending in the Milagro Clinic and the Intermediate Care Nursery-3. Her previous research includes the introduction and assessment of group prenatal care.

Sherry Weitzen, MD, PhD is an Assistant Professor/ Attending Physician in Family Medicine at UNM. She graduated from the Sackler School of Medicine in Tel Aviv, and completed her family medicine residency at UNM. Prior to medical school, she was a public health researcher at Brown University. She now attends in the Intermediate Care Nursery and in the FOCUS program.

Sarah Gopman, MD is an Associate Professor/ Attending Physician of Family Medicine at UNM. She received her medical degrees from the Oregon Health Science University School of Medicine in Portland in 2000. She graduated from the UNM Family Medicine Residency Program, and then completed a Maternal and Child Health Fellowship in our department. She attends in the Milagro clinic and on the Maternal and Child Health Service, as well as in the Intermediate Care Nursery-3.

Larry Leeman, MD, MPH received his medical degree from University of California, San Francisco in 1988, completed residency training in Family Medicine at UNM, and an obstetrics fellowship from the University of Rochester. He directs the Family Medicine Maternal and Child Health service and fellowship and co-medical director of the UNM Hospital Mother-Baby Unit, and is Medical Director of the Milagro Program. Areas of research include rural maternity care, pelvic floor outcomes after childbirth, family planning, and vaginal birth after cesarean (VBAC).

Ariele Bauers, CNM, is a midwife who works in outpatient Milagro clinics and also provides newborn and postpartum care on the Family Medicine Maternal Child Health Service. She has cared for numerous Milagro families through the neonatal withdrawal process in her two years at UNM.

9.2. When applicable, describe which licensed physicians/providers will be responsible for medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics.

Resident and attending physicians currently practicing in the newborn nursery, Mother Baby Unit, and the ICN-3 will be responsible for medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics. They will be expected to follow the already established clinical protocols. The research team will inform the primary medical team

which opiate (methadone or morphine) will be used to treat infants enrolled in the study at the time of initiation of therapy.

9.3. Describe other resources available to conduct the research: For example, as appropriate:

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

  As described above in the power calculation, there are approximately 78 newborns a year on our service with in-utero methadone or heroin exposure. Assuming not all of these infants would be participants, we estimate that it would be possible to recruit 60 infants for a pilot study within a year. After conducting the study for a year, our withdrawal and birth rates were lower than expected, therefore we are requesting a modification to extend the study to 2 years total with approximately 100 recruited infants.

- *Describe the time that will be devoted to conducting and completing the research.*

  Recruitment will be on a rolling basis over a year as infants are born. We estimate an additional 6 months for data analysis. During the study period, time would be spent conducting consent conversations and collecting data from the electronic medical record. Once the study is complete, time will be spent analyzing the data for trends.

- *Describe the facilities available to conduct the research.*

  The primary facility is UNM Hospital.

- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*

  Assigned social workers are present on Labor and Delivery, Mother Baby Unit, and ICN-3, and are available to meet with all families. Families also have access to a community health worker (Michele Wooton) in the Milagro Clinic who helps women access social services and arrange counseling prenatally and postpartum. A primary nurse is available to answer questions and concerns regarding infants being treated for NAS in all of the hospital units.

- *Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

  Core research staff will meet to discuss the protocol prior to study initiation. The protocol will also be presented at a department-wide continuing medical education conferences (Family Medicine Resident School, Pediatrics Resident School) so that resident physicians are adequately informed about the protocol, research procedures and their duties. During many weeks core research staff will be attending physicians on the Maternal Child Health Service, Newborn Nursery service or ICN-3 and will be caring for the patients involved in the study. During weeks in which other physicians are attending on these services, core research staff will reach out to supervising

physicians on these services to discuss any potential issues that may arise via email or in person meeting.

- *If CTSC resources are being accessed, the signed CTSC resources attachment must be uploaded on the CTSC Submission page in Click.*

10. Prior Approvals

1.1. Describe any approvals that will be obtained prior to commencing the research. (e.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

1.2. Upload the required Departmental Review Form signed by your Department Chair (or authorized designee if the PI is the Department Chair) into Click under "supporting documents."

1.3. If a study includes ionizing radiation, the Radiation Safety Attachment (HUS-FORM_1) must be uploaded (attached) in Click with your submission. The consent should include radiation exposure information in the Risks section.

1.4. If applicable to the study, include the signed "Biological Specimens" and/or "Drug Attachment" in Click with your submission.

2. Multi-Site Research

1.1. If this is a multi-site study where the UNM HSC PI is the lead investigator, or UNM HSC is the coordinating site, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators will conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

1.2. Describe the method for communicating to engaged participating sites:

- *Adverse events*
- *Problems*
- *Interim results*
- *Data and safety monitoring reports*

- *The closure of a study*

1.3. If the UNM HSC investigator is serving as the "sponsor-investigator" of a FDA-regulated trial, describe how sponsor responsibilities will be fulfilled, including, but not limited to:

- *Trial Monitoring*
- *Investigational Product Accountability*
- *Safety and other interim reporting to investigators and FDA*
- *Unanticipated Problem reporting to investigators, IRBs, and FDA*

This is not a multi-site study.

12. Study Procedures

1.2. Describe, in chronological order, all research procedures and interventions being performed and when they are performed. Include:

- *Each specific intervention, procedure, examination, imaging, laboratory test, etc. that subjects will undergo for the purposes of the research and the purpose of it.*
- *Each drug, biologic, device, or other such product used in the research, the purpose, and the regulatory status (e.g., investigational, marketed – on label, marketed – off label, etc.)*
- *Each survey, questionnaire, interview, focus group, etc., that subjects will be asked to complete or participate in for the research and the purpose of it.*
- *Each data source that will be used to gather information about subjects and the purpose of it (confidentiality will be addressed later.*
- *Indicate whether subjects would already be expected to undergo any of the procedures for clinical, diagnostic, or other non-research purposes*
- *Include all referenced study instruments, such as questionnaires, scripts, diaries, and data collection forms with your submission as separate attachments.*

At the first clinic visit or at presentation to OB Triage for opiate replacement therapy, clinicians routinely discuss hospital policy regarding NAS treatment for all women requesting treatment for opiate dependence in pregnancy.

When women are admitted to Labor and Delivery and/or up to 12 hours postpartum, research staff will approach patients about study enrollment. Women will be approached for study enrollment if their medication list on admission includes methadone, if they self-report methadone use prenatally, if their urine drug screen is positive for methadone and/or opiates on admission and is negative for buprenorphine.

Research staff will use a standardized script at enrollment (Attachment: Consent script.)

If women choose to enroll in the study, and their infants require treatment for NAS, their infants will be randomized and assigned a study number for treatment using the methadone or morphine protocols at the time treatment is required (Attachment: NICU NAS pharmacy protocol) We are choosing to consent more parents or guardians of infants than will ultimately participate fully in the study because we know that about 75% of infants exposed to opiates other than buprenorphine will require medications for withdrawal, and it is possible that the time for initiation of medication may be after hours. Therefore the consent process occurs at a non-stressful time for parents/ guardians, and the primary medical team for the infant can quickly initiate therapy when needed.

All infants will be monitored for signs of withdrawal using the standard UNM NAS scoring protocol (Attachment: NICU NAS pharmacy protocol). Standard of care at UNM is to treat infants exposed to methadone or heroin in-utero with methadone if they require pharmacologic therapy for NAS, therefore treatment will not be withheld if they choose not to enroll in the study. Standard of care is also to obtain a urine drug screen on all infants with reported exposure to opiates in pregnancy. Enrolled patients will thus undergo routine urine drug screening. The only difference from standard care with regards to the study protocol is the treatment of half of the methadone or heroin exposed infants with morphine. The morphine protocol is proven for safety and efficacy currently in buprenorphine exposed infants at the University of New Mexico, and for all opiate exposed infants in many other institutions.

Randomization will occur by a stratified method in groups of six to ten participants to attempt to control for prenatal exposure (heroin or methadone).

Infants randomized to receive methadone will receive treatment using our standard Methadone Withdrawal Protocol (Attachment: NICU NAS pharmacy protocol).

Infants randomized to receive morphine will receive the drug using the standard Morphine Withdrawal Protocol (Attachment: NICU NAS pharmacy protocol).

If at any time in the study, infants require transfer to higher level of care in the Neonatal Intensive Care Unit (excluding an initial 24 hour transition period after birth), they will become excluded from the study and data collection on these infants will stop. These infants will continue to receive the standard of care therapy as determined by the Neonatal ICU team. If infants require transfer of care to the Intermediate Care Nursery-3 from Mother Baby Unit or Carrie Tingley Inpatient Unit, they will continue to be enrolled in the study and data collection will continue until hospital discharge. In our current experience, the number of infants needing transfer is minimal, and in most cases involves transfer from a floor unit to the ICN-3. It is very rare to require transfer to the NICU for neonatal abstinence syndrome after treatment has been initiated. Infants requiring initial NICU admission for less than 24 hours for a non-withdrawal related reason (i.e. cardio/respiratory transition related to birth, hypoglycemia related to maternal diabetes, etc) will be included in the study if they are able to transition to the ICN-3 or Newborn Nursery within 24 hours after birth.

Physicians and nurses cannot feasibly be blinded to the study drug due to differences in drug administration times for methadone vs morphine as described in the protocols above.

Newborn outcomes, including length of hospital stay, length of treatment (defined as number of days on opiate replacement therapy) will all be collected through the electronic medical record and recorded in a password protected database. Please see the attached data collection form for all outcomes.

At hospital discharge, parents will be asked to complete the HCAHPS patient satisfaction tool, which is a standard, validated instrument of hospital satisfaction (Attachment: HCAHPS tool).

13. Data Analysis

1.3. Describe the data analysis plan, including any statistical procedures.

1.4. Provide a power analysis

Data will be analyzed using STATA 13.0. Continuous variables will summarized as means or medians. Differences in maternal and neonatal characteristics between methadone and morphine groups will be compared using bivariate analyses. Length of stay will be summarized as mean and median, and the length of stay will be compared between the morphine and methadone group using parametric and non-parametric methods. Multivariable regression analyses will be used to estimate the effect of morphine versus methadone on length of stay, controlling for pretreatment differences in maternal and neonatal characteristics between treatment group.

Based on obtained sample size, and difference in length of stay between groups, the standard deviation of the difference, and type I error set at 0.05, we will determine the power of the difference estimate. These statistics will be used for sample size determination for planning of future studies.

2. Provisions to Monitor the Data to Ensure the Safety of Subjects

This section is required when research involves more than Minimal Risk to subjects. Describe:

2.1. The entity (e.g., DMC, DSMB) or individuals (e.g., medical monitor) who will perform data and safety monitoring. Describe whether they are independent of or affiliated with the sponsor or investigator. If a DMC or DSMB is planned, describe the composition of the committee or board. Generally, a DSMB or DMC should be composed of experts in all scientific disciplines needed to analyze and interpret the data (e.g., epidemiologists, biostatisticians, subject matter experts).

2.2. The safety information that will be collected and monitored.

2.3. The frequency or periodicity of review of data, such as specified points in time or after a specific number of participants have been enrolled.

2.4. The plans for review of scientific literature and data from other sources that may inform the safety or conduct of the study.

2.5. The procedures for analysis and interpretation of the safety data.

2.6. The conditions that would trigger a suspension or termination of the research (i.e., stopping rules), if appropriate.

2.7. The plan for reporting findings to the sponsor, investigators, and HRRC.

A Data and Safety Monitoring Plan will be developed and will be led by Dr. Andrew Hsi at the University of New Mexico. Dr. Hsi is an expert in the field of neonatal abstinence syndrome. Dr. Hsi will monitor the study approximately every 3 months. The report on the Data and Safety Monitoring Plan at Continuing Review will include enrollment and dropout rates, protocol deviations, review of subject symptoms, and preliminary analysis of the primary outcome (newborn length of stay.)

3. Withdrawal of Subjects

3.1. Describe any anticipated circumstances under which subjects may be withdrawn from the research without their consent.

Infants will be withdrawn if they develop a serious medical comorbidity (eg intubation/ventilation, serious allergic reaction) or require transfer to the neonatal intensive care unit.

3.2. Describe any procedures for orderly termination/safe withdrawal (e.g., tapering of meds, physical exams, laboratory or other tests, etc.).

This is not applicable to our study. If an infant is withdrawn from the study voluntarily or for the above reasons, they will continue to receive the standard of care therapy but data collection will stop.

3.3. Describe any procedures for partial withdrawal (e.g., from procedures but allowing continued data collection by record review, phone contact, etc.).

This is not applicable to our study. If an infant is withdrawn from the study voluntarily or for the above reasons, they will continue to receive the standard of care therapy but data collection will stop.

3.4. Describe the disposition of existing data/specimens when a subject withdraws. Describe any restrictions on a subject's ability to withdraw any already gathered data or specimens (e.g., unable to retrieve because it has been stripped of identifiers and no code exists to allow re-linking). (Note: FDA requires that existing data be maintained for studies subject to FDA oversight.)

If an infant is withdrawn from the study, all of the data related to that individual will be discarded. Data collection will occur upon hospital discharge of the infant, therefore there is not a risk of not being able to retrieve data.

3.5. Describe withdrawal procedures and any limitations in the consent document.

Please see the consent document for specific information (Attachment 4.)

4. Data Management/Confidentiality

4.1. Indicate how the research team is permitted to access any sources of information about the subjects. Note whether the research requires the access, use, or disclosure of direct identifiers (e.g., name, medical record number, etc.)

The research team will access data from infants' medical record through password protected Powerchart access, and enter data into a password-protected database.

4.2. Note whether the research requires the access, use, or disclosure of Protected Health Information.

The research team will have access to protected health information through Powerchart.

4.3. Note whether the data includes information that may be considered sensitive or require additional protections such as HIV, genetic test results, mental health information, substance abuse information, criminal records, etc.

Mother's history of substance abuse will be collected and is a requirement for study enrollment.

1.1. Indicate whether a Certificate of Confidentiality will be used to protect data from forced release (e.g., subpoena) and whether the certificate is in place or will be applied for once IRB approval is in place. More information on Certificates of Confidentiality is available here: http://grants.nih.gov/grants/policy/coc/index.htm

A certificate of confidentiality will be obtained once IRB approval is in place through the National Institute on Drug Abuse regarding the mother's substance abuse history.

4.4. Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, transmission and transport.

All study documents will be stored in a locked filing cabinet in the principal investigator's office. Electronic data will be stored on a secure server at the University of New Mexico Health Sciences Center used to repose data entered using the REDCap database platform. No data will be stored on a laptop computer or on any thumb drive.

4.5. If data will be coded, describe the nature of the code and mechanisms that will be used to protect the code (e.g., secure storage, limited access, separate location from research data).

Identifying data will be removed after data collection and referable only by a study number. The primary investigator will keep the code connecting the data and the participant in a locked office. All study records will be kept for three years from the start of the study, de-identified, on password protected computers in a locked office.

The study's link between participant and study number will be kept separate from data and specimens, and the link will be destroyed when the study is closed through the HRPO.

4.6. Describe any procedures that will be used for quality control of collected data.

Approximately every 3 months, collected data will be randomly re-inspected by an additional member of the study team to ensure quality control.

4.7. If data will be transferred or transmitted to outside locations or entities, describe:

- *What information will be included in that data or associated with the specimens?*
- *Where and how data or specimens will be stored?*
- *How long the data or specimens will be stored?*
- *Who will have access to the data or specimens?*
- *Who is responsible for receipt or transmission of the data or specimens?*
- *How data and specimens will be transported?*

N/A, data will not be transferred to outside locations or entities.

1.10. Describe if data will be collected, transmitted, and/or stored via the internet, the identifiability of the data, and the security measures that will be employed to protect it.

Data will be collected, transmitted and stored via the intranet. The data will be de-identified upon collection from the electronic medical record. The data will be stored only on a shared protected drive on the intranet.

1.1. Describe if data will be collected by audio or video recording, how the recordings will be secured, whether and when recordings will be transcribed, if the transcription will include identifiers, if, when, and how the recordings will be deleted. Describe if the subjects will have the opportunity to review the recordings and request full or partial deletion. If the recordings may include persons other than the subjects, describe how this will be managed.

N/A

1.2. Describe if the data will include photographs, what will be included in the photographs, and how the photographs will be secured. Describe if subjects will have the opportunity to review the photographs and request destruction. If the photographs may include persons other than the subjects, describe how this will be managed.

N/A

2. Data and Specimen Banking

4.8. If data or specimens will be banked or archived locally for future use, provide the name and IRB number of the repository that they will be deposited into. Describe exactly what data or specimens will be banked and for what purposes, and whether the data or specimens will include identifiers, be coded, or be fully stripped of all identifiers with no code or key that would allow relinking. Be certain to describe the banking in the primary consent. A separate consent and authorization, if applicable, will be necessary for the banking activity itself and is typically provided by the repository. If you need to establish a repository for the purposes of banking or archiving data or specimens, a separate submission for the repository is needed as this is considered to be a distinct research activity under the regulations.

N/A

4.9. If this is a multi-center study, and/or if data or specimens will be banked or archived elsewhere, identify who the holder of the data or specimens will be, exactly what data or specimens will be banked and for what purposes, and whether the data or specimens will include identifiers, be coded, or be fully stripped of identifiers with no code or key that would allow relinking. A Materials Transfer or other agreement may be necessary, please consult with the HSC Sponsored Projects Office at 505-272-6264 or by email at hsc-preaward@salud.unm.edu. Material Transfer Agreement procedures may be found at http://hsc.unm.edu/financialservices/preaward/ancillary-agreements/material-transfer-agreements/procedures.html. Be certain to describe the banking in the consent and authorization, using opt-in procedures, and the procedures for subjects to request withdrawal of their data or specimens and any limitations on their ability to do so.

N/A

5. Risks to Subjects

5.1. List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Describe the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. Note that almost all research includes confidentiality risks.

5.2. If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

5.3. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If pregnancy testing or birth control provisions are required, describe these.

5.4. If applicable, describe risks to others who are not subjects.

5.5. Describe the steps being taken to mininize the probability or magnitude of risks.

Note: All risks described here should also be described in the consent document.

There are risks of stress and inconvenience for parents who participate in the research study as they will be asked to complete a patient satisfaction survey at the end of their child's hospitalization. There are also risks of possible loss of privacy and confidentiality. For this reason, a Certificate of Confidentiality will be obtained from NIDA, and all data will be kept confidential and deidentified.

The study will use existing protocols for the treatment of neonatal abstinence syndrome with either methadone or morphine. The experimental component of the study is the use of the morphine protocol for a different exposure group (in-utero methadone or heroin). For this reason, there are minimal foreseeable medical risks of treatment. Please see the consent document for details on minimizing risks to subjects.

6. Potential Benefits to Subjects

6.1. Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

6.2. Indicate if there is no direct benefit. Do not include benefits to society or others in this section.

Note: All potential benefits described here should also be described in the consent document.

Possible benefits to subjects include decreased length of stay and improved parental satisfaction. Given the decreased length of stay observed for infants currently treated with morphine rather than methadone (in-utero exposure to buprenorphine), we expect a decreased length of stay in the study population (in-utero exposure to methadone or heroin).

7. Recruitment Methods

7.1. Describe when, where, and how potential subjects will be recruited.

7.2. Describe the methods that will be used to identify potential subjects (e.g., chart review, referral, etc.).

7.3. Describe materials that will be used to recruit subjects (e.g., emails, scripts, advertisements, brochures, flyers, etc.). Attach draft copies of the documents or audio or video recordings with the application. Once the draft has been approved, the final copy of the printed material, audio or video recording must be submitted for review and approval prior to implementation. Please see Worksheet HRP-315 for information on advertisement standards.

Candidates will be identified and recruited based on eligibility criteria. Prior to delivery, possible candidates will be identified by review of the Milagro prenatal substance abuse clinic census. After identification by the primary medical team by chart review, women will be approached by the research team upon admission to Labor and Delivery, or up to 12 hours after delivery at UNM Hospital in the Labor and Delivery, Mother-Baby, Newborn Nursery, or Intermediate Care Nursery-3 Units. When possible, families will be approached to discuss the study within standard business hours. The recruitment script detailed in the study protocol will be used to describe the study to patients. (Attachments: Recruitment script, Waiver of consent for screening/recruitment purposes)

8. Provisions to Protect the Privacy Interests of Subjects

8.1. Describe the steps that will be taken to protect subjects' privacy interests. "Privacy" refers to persons and their interest in controlling the access that others have to themselves. For example, based on their privacy interests, people may want to control:

- *The time and place/setting where they are examined or provide information*
- *The nature of the information they provide*
- *The nature of the experiences they are exposed to*

- *Who may observe or have access to information about them*

  For example, individuals may not want to be approached for participation, provide responses to a research interview, or undergo a research procedure in a location where they may be seen or overheard.\

1.2. Describe the steps that will be taken to protect subjects' privacy including privacy protections during recruitment, consent, and data collection. Issues related to data are addressed in the Data Management/Confidentiality Section.

Procedures for protecting against or minimizing the likelihood of loss of privacy include approaching parents or guardians privately and using a private room to answer test questions. The treatment plan for the baby will be kept confidential, and discussion regarding treatment protocols would occur according to routine protocols. Conversations can occur in a private room in Labor and Delivery, the Mother Baby Unit or Carrie Tingley Hospital. There are no private rooms in ICN-3, so efforts will be made to create a confidential, quiet space in this clinical environment (eg a quiet corner in the unit, away from other parents visiting their newborns, or in a separate conference room away from the unit.) Information that is collected will be labeled with a study number and kept in a secure locked file. Information that will be entered in to a database will only contain the study number. Subject's research data and study records will be maintained until the youngest subject turns 22 years old.

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2. Economic Burden to Subjects

8.2. Describe any costs that subjects may be responsible for because of participation in the research. Clearly stipulate what procedures are standard of care and what procedures are research-related in the table below. Please place an X in the box for the responsible party for each procedure involved.

List any costs to participants (or their 3rd party payer); include any charges for study procedures, visits, or drug/devices.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**

Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**

1.2. List any other costs to participants not already described above.

8.3. Indicate whether subjects will be charged for investigational drugs, devices, procedures

8.4. Explain who will be responsible for paying for treatment of adverse events

8.5. Ensure that the cost section of the consent form reflects the cost that are covered by the sponsor and the costs for which the subjects (or 3rd party payers) are responsible.

There will be no additional cost to the parents or guardians of test participants other than the routine hospitalization costs for standard of care. All charges related to hospitalization including urine drug screens and therapy with either methadone or morphine are considered to be standard of care and will therefore be billed to the patient's insurance company (3rd party payer).

23. Compensation

8.6. Describe any plans for compensation or reimbursement for subjects (amounts, methods (e.g., cash card), and payment schedule). Describe why the proposed amount is reasonable and appropriate for the subjects' time and inconvenience. Credit for payment should be prorated and not be contingent upon the participant completing the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise

would have withdrawn. Note: Consult with your department official for reporting requirements associated with cash or merchandise cards distributed to research subjects.

Participants will be compensated with $20 Walmart merchandise cards.

9. Compensation for Research-Related Injury

9.1. If the research involves more than Minimal Risk to subjects, describe the plan for compensation in the event of research related injury.

9.2. If subjects are responsible for seeking their own form of care for research-related injury, describe how this will be communicated and what options are available to participants.

The research uses already existing protocols and therefore does not pose more than minimal risk to subjects, as such we do not anticipate any research related injury.

10. Consent Process

10.1. Indicate whether you will you be obtaining consent, and if so describe:

10.1.1. Who will be responsible for obtaining consent and their qualifications/training to do so. Be certain to identify which study team members will obtain consent in Click under Project Contacts.

10.1.2. Where will the consent process take place and the provisions for privacy.

10.1.3. The steps that will be taken to minimize the possibility of coercion or undue influence

10.1.4. The waiting period available between reviewing the study and consent with the potential subject and obtaining the consent.

10.1.5. Processes to ensure ongoing consent throughout the study.

10.1.6. Any steps that will be taken to enhance understanding

10.1.7. Any procedure/testing for ensuring that the consent is understood by the potential subject (e.g., teach back)

The infant's care provider will approach the parent or guardian to introduce and discuss the study. If the infant's parent or guardian chooses to participate, a co-investigator will perform the consent process. The consent is structured such that the information regarding the study is provided in an unbiased manner in order to promote independent and thoughtful decision-making and in order to avoid coercion or undue influence.

Parents or guardians of eligible infants will be recruited and consented during routine business hours, during their inpatient stay at UNMH upon admission and up to 12 hours after delivery. For both groups, the study will be introduced, questions answered, and consent obtained. The parents or guardians of the subjects will be given a copy of the consent prior to leaving the clinic

or hospital. The signed consent form will be stored and secured in a locked filing cabinet in the principal investigator's office.

HIPAA authorization will be obtained using the standard HRPO HIPAA authorization form.

Subjects not fluent in English

10.1.8. Indicate what language(s) other than English are understood by prospective subjects or representatives.

10.1.9. If you anticipate enrolling subjects who do not understand or have limited fluency in English, describe the process to ensure that the oral and written information provided to those subjects initially and throughout their participation will be in the language they understand (e.g., use of translations and interpreters). Please note that translations of consent documents and subject materials will likely be required once the content of the English-language version is approved.

1.1.1. Short-form consent documents are available for unanticipated enrollments of persons who don't understand or have limited fluency in English. However, based upon the nature of the research (e.g., clinical trials) subsequent translation of the consent document may be required so that the subject has access to written information about the research in a language they understand.

Based on our current population of Milagro patients, non-English speaking families will represent very few or none of our study pool. A short-form Spanish consent will be requested from translation services in the case of unanticipated Spanish speaking families. If additional translation of consent documents is required in this scenario, subsequent translation will be requested at the time of need.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

1.1.2. The IRB must specifically approve the enrollment of adults unable to consent and adults with cognitive impairment or limited decision-making capacity. Complete the applicable checklist in the Checklists Section of this Protocol Template.

1.1.3. Describe whether the entire subject population or a portion of it is expected to have limited or no ability to provide legally effective consent.

1.1.4. Describe the process to determine whether an individual is capable of consent.

1.1.5. Describe the process to determine whether a prospective subject is capable of providing consent. Include who will be responsible for determining capacity and how it will be documented.

1.1.6. Describe how the participant's decisional capacity will be assessed as the study proceeds in order to evaluate any fluctuation in the participant's level of capacity to consent.

1.1.7. If it can be anticipated that some or all subjects will regain capacity to provide consent, describe the provisions to provide them with information about their

participation in the research and to seek their consent for ongoing participation, if applicable.

1.1.8. For research conducted in New Mexico, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative."

1.1.9. For research conducted outside of the New Mexico, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research.

1.1.10. Describe how the representative's authority to provide consent will be confirmed.

1.1.11. Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent.*

Subjects who are not yet adults (infants, children, teenagers)

1.1.21. Provide the age range of the children anticipated to be enrolled in the research.

Study participants are newborn infants.

1.1.12. Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted.

- *For research conducted in New Mexico, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*
- *For research conducted outside of New Mexico, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted.*

1.1.23. Describe whether parental permission will be obtained from:

- *One parent (may be permissible, if the IRB approves, for (1) research not involving greater than minimal risk, or (2) research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects)*

Parental or guardian permission will be obtained by one parent or guardian as this research only poses minimal risk.

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of*

the child. (Permissible for research involving greater than minimal risk and no prospect of direct benefit to individual subjects.)

1.1.24. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent.

In the case of parental right revocation by NM Children, Youth and Families Department, the legal guardian assigned to the child would be approached for consent.

1.1.13. Indicate whether the children to be enrolled in the research should be capable of providing assent.

1.1.14. Indicate if assent will be obtained from all, some, or none of the children and provide justification. If assent will be obtained from some children, indicate which children will be asked for assent.

1.1.15. When assent of children will be obtained describe the proposed assent process and whether and how assent will be documented. The assent process and documentation of assent should be age-appropriate and may consist of different procedures for different age groups.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

- *Complete the applicable checklists in the Checklists section of this Protocol Template if you are requesting a waiver or alteration of consent for this research*
- *Consent can be waived for all of some subjects (e.g., the research includes a retrospective cohort)*
- *Consent can be waived in full or in part (e.g., partial waiver for recruitment purposes)*

26. Documentation of Consent

2.1. Describe if you plan to use a consent form to document consent. Use the UNM HSC consent generator or one of the consent templates available on the HRPO website. Attach consent documents as fully editable Word documents (i.e., please don't submit protected documents or pdfs). Please include page numbers in the footer (e.g., Page 1 of XX).

2.2. If the study is collecting and/or storing tissue samples, include a Tissue Banking Consent Form (and Authorization if the specimens will be accompanied by PHI).

2.3. Describe if you plan to obtain consent but will be using a script, information sheet, or other mechanism. If you will obtain consent verbally, attach a consent script and information sheet, if you will be providing one. If you will be obtaining consent via an on-line survey, please use the survey cover letter consent template on the HRPO website and include your email script with your submission.

Complete the checklist for "Waiver of Documentation of Consent" in the Checklists section of this Protocol Template. If you will be excluding or modifying one or more of the required elements of consent you will also need to request an Alteration of Consent.

The consent process will take place using a standard script (Attachment 1), as well as the combined HIPAA/ consent form which is included as an attachment (Attachment 5). Tissue samples will not be collected.

3. Study Test Results/Incidental Findings

3.1. ***Individual Results:*** *Indicate whether you intend to share study test or procedure results with study participants If so, describe which results will be shared, whom the results will be shared with (e.g., subjects, parents, primary care physicians), and how the findings will be communicated (e.g., in person consultation, posting in medical record, etc.). If the findings are the results of laboratory tests, indicate whether the tests will be processed in a CLIA-certified lab.*

The primary medical team will be responsible for sharing infant progress with families in person during routine patient care rounds, which are part of the current standard of care (NAS scores, expected weaning dates, and expected length of treatment.)

3.2. ***Incidental Findings:*** *Based upon the nature of the research, and the tests that will be performed, indicate if you anticipate that the research may result in incidental findings (traditionally defined as results that arise that are outside the original purpose for which the test or procedure was conducted (for example, a potential tumor is identified but this is not the reason imaging was obtained). If so, please describe your plans for communication of such results to subjects and their health care providers, if appropriate. If there are limitations on the accepted validity of the results (e.g., test performed in non-CLIA lab, test available in the context of research only), please describe and provide a plan for confirmatory testing or justification for why it is not recommended, not necessary, or not possible. If you do not plan to provide results, provide justification.*

- *Be certain to describe your plans for provision of study results and incidental findings in your consent documents.*
- *For more information on incidental findings, please consult the President's Bioethics Commission Report "Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts": http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf*
- *For information specific to Whole Genome Sequencing, please consult the President's Bioethics Commission Report "Privacy and Progress in Whole Genome Sequencing": http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf*

We do not anticipate any incidental findings from our research protocol as it is already in use for the buprenorphine exposed infant population.

28. Sharing Study Progress or Results with Subjects

3.3. Describe whether you intend to provide subjects with a summary of the trial progress while the study remains underway. If so, describe your plans and the mechanisms that you will use (e.g., newsletter, handouts, mailings, etc.). Please note that all written materials that will be provided to subjects need to be reviewed and approved by the IRB prior to use.

3.4. Describe whether you intend to provide subjects with a summary of the study results after the study is complete. If so, indicate if the information will include study arm assignment if the study involved blinding. Please describe your plans for dissemination of results and the mechanisms that you will use. Please note that IRB review of materials may be required, consult with the HRPO prior to distribution.

Study progress will be shared with participants at the conclusion of the study via a mailing.

4. Inclusion of Vulnerable Populations

4.1. If the research involves individuals who are vulnerable to coercion or undue influence, describe who will be included, why their participation is necessary or warranted, and any additional safeguards included to protect their rights and welfare. The following is not intended to serve as a comprehensive list, rather to provide some examples for your consideration.

4.1.1. If the research includes students or employees, describe protections to promote the voluntary nature of participation and minimize the risks associated with access to or use of data by persons in a position of actual or perceived authority.

4.1.2. If the research includes economically disadvantaged persons, describe the mechanisms to promote the voluntary nature of participation and to minimize economic risks associated with participation.

4.1.3. If the research includes educationally disadvantaged persons, describe the mechanisms to ensure that they are provided information and materials that enhance their ability to understand the research initially and throughout their participation in the research.

4.1.4. If the research includes seriously or terminally ill patients, describe the mechanisms to ensure that they understand the true purposes of the research, the risk it entails, and what is known or not understood about the likelihood of individual benefit

4.1.5. If the research involves pregnant women, note this here and complete the Pregnant Women Checklist in the Checklist Section of this Protocol Template.

4.1.6. If the research involves neonates of uncertain viability or non-viable neonates, note this here and complete the applicable checklist in the Checklist Section of this Protocol Template.

Note: For the purposes of the federal research regulations, viability is established shortly after delivery. "Viable, as it pertains to the neonate, means

being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration." Once a neonate has been determined viable, they are considered a child under the regulations.

4.1.7. If the research involves prisoners, note this here and complete the Prisoners Checklist in the Checklist Section of this Protocol Template.

4.1.8. If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), note this here and complete the Children Checklist in the Checklist Section of this Protocol Template.

4.1.9. If the research involves cognitively impaired adults, note this here and complete the Cognitively Impaired Adults Checklist in the Checklist Section of this Protocol Template.

Our research involves infants. Due to the sensitive nature of our perinatal substance abuse population, we will pursue a Certificate of Confidentiality from NIDA and will discuss this with patients during the consent process.

5. Community-Based Participatory Research

5.1. Describe involvement of the community in the design and conduct of the research. If members of the community will fulfill key research responsibilities such as recruitment and consent, describe what research activities community members will be responsible for, how they will be trained, and the plan for quality oversight. When relevant, please include information regarding the approval of the research at collaborating sites (e.g., Albuquerque Public Schools).

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

N/A

6. Research Involving American Indian/Native Populations

6.1. Please provide detailed information of the local research context including how the research questions are sensitive to community attitudes and how the PI has ascertained that the proposed research is acceptable to the local population in terms of tribal regulations, applicable law and standards of professional conduct and practice. Attach any supporting documents from tribal officials or entities addressing the status or requirements for review of the research activity from tribal officials or tribal entities (for example, Indian Health Services, the Navajo Nation IRB).

N/A

7. Transnational Research

7.1. When conducting transnational research, you must ensure that subjects are provided equivalent and appropriate protections for human subjects located outside of the United States. Please refer to the following website for current OHRP interpretations of research standards, equivalent protections, and for a current compilation of international research standards and regulatory agencies. http://www.hhs.gov/ohrp/international/index.html

7.2. ***Location:*** *Describe the research locale and how and why the setting was chosen. Describe significant cultural norms, local laws, and differences with U.S. culture with respect to autonomy, perception of research, recruitment, consent, age of majority, parental permission, etc.*

7.3. ***Study Personnel:*** *Describe the qualifications of the researcher and research team to perform research in the community/culture where it will occur. Indicate the research team's ability to speak, read, and write the language of the subjects. Describe the researcher's knowledge of or expertise in local or state laws, culture, and community norms. Indicate if the researcher was invited into the community (provide documentation, if available). If not invited, then describe how the researcher will have culturally appropriate access to the community.*

7.4. ***Consent:*** *Describe the consenting procedure that you intend to use for the research and why it is appropriate for the community where the research will occur. Describe how you will ensure that potential subjects understand the research, and the voluntariness of their participation.*

7.5. ***Community Consultation:*** *Describe any plans for community consultation to assess receptiveness to the proposed research and to obtain feedback on how it should be conducted and any limitations or boundaries that should be respected. Describe plans for dissemination of results to subjects and to the community.*

N/A

8. Drugs or Devices

8.1. If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

8.2. If the drug is investigational (has an IND), identify the holder of the IND/IDE/Abbreviated IDE.

8.3. For research involving drugs, complete and attach a signed "Drug Attachment", available in Click or the HRPO website

8.4. For research involving devices, complete the "Device Checklist" in the Checklist Section of this template.

This study will involve only morphine or methadone, which are currently in use as part of accepted and standard of care protocols. Morphine is widely used for the treatment of neonatal abstinence syndrome nationwide, and is currently used for all neonates with NAS exposed to

buprenorphine in utero at UNMH. Medication accountability and labeling and dispensing will be conducted in accordance with standard University Hospital Pharmacy protocol. Security safeguards in place to ensure proper accountability, access, and medication storage include standard safeguards in place by University Hospital Pharmacy. These safeguards will prevent accidental use outside of the approved research study.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

Medical records will be reviewed to determine mothers in the Milagro prenatal substance abuse program who are currently receiving medication assisted therapy with methadone or are known to be using other opiates.

2. Describe the purpose for the review (e.g., screening):

The review of medical records will be for screening to determine potentially eligible families to approach for consent at the time of delivery in the hospital.

3. Describe who will conducting the reviews (e.g., investigators, research staff):

Co-investigators will conduct the reviews. All of the co-investigators are also physicians involved with the Milagro substance abuse program.

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

Yes All persons conducting the reviews have permitted access to the data source as physicians treating this population.

No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

True

Other justification:

b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

True

Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

True

Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

True

Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   Yes. Describe: A list of eligible patients and their estimated due dates will be maintained in order to efficiently organize efforts for recruitment and approach for consent when women are hospitalized for birth. This list is already maintained by the Milagro clinic staff for purposes of clinic tracking and distribution of gifts when women deliver their babies.

No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   The list is currently maintained by medical record number and is accessible only to Milagro staff and physicians. MRNs will need to remain in place until women are approached for consent so that they can be identified when they present in labor. After women are approached for participation in the study and accept or decline, their medical record number and other information will be deleted from the list.

1. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   True

   False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   All

   Some. Explain:

2. Provide justification for one of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

1. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   Yes. Please attach a copy to your submission in Click.

   No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

Note: FDA-regulated research is not eligible for an alteration of consent.

1. Which element(s) of consent do you wish to eliminate and why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are

commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?

   All

   Some. Explain:

1. Provide justification for each of the following regulatory criteria:

   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   All

   Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service

programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   All

   Some. Explain:

1. Describe your plan to protect health information identifiers from improper use and disclosure:

2. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

3. Describe why the research could not practicably be conducted without the waiver or alteration:

1. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   True

   False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

XX **Research not involving greater than minimal risk**. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, or EPA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

_____

1. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

2. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates

Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates

Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

1. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

True

False

1. The research will not terminate the heartbeat or respiration of the neonate

True

False

2. There will be no added risk to the neonate resulting from the research

True

False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name:

B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?

Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

No

D. Is the research IDE-exempt?

Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

No

E. Does the research involve a Non-Significant Risk (NSR) Device?

Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf