AIM 2- Prevention of Neonatal Abstinence Syndrome

Study Protocol

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Aim 2: PREVENTION OF NEONATAL ABSTINENCE SYNDROME (NAS2)

Contents

1.0 Background and Purpose

The misuse of and addiction to opioid medications has become the most rapidly increasing drug problem in the US, which has consequences for pregnant mothers and their babies. The prevalence of maternal opioid drug use at the time of delivery in California is approximately one percent. The neonatal abstinence syndrome (**NAS**) is a constellation of narcotic drug withdrawal symptoms that develops in 42 to 94 percent of infants born to narcotic dependent mothers. There are no preventative treatments for this severe syndrome, which can result in a prolonged hospitalization and treatment in a neonatal intensive care unit.

Based upon a genetic discovery, we demonstrated that administration of a 5-HT3 antagonist (ondansetron) prevented the symptoms of narcotic drug withdrawal in experimental studies in mice and in humans. From this, we hypothesize that ondansetron administration to pregnant narcotic-using mothers just prior to delivery, followed by a 3 to 5-day period of ondansetron

administration to the neonate, could reduce the incidence or severity of NAS symptoms. Ondansetron is a broadly utilized drug with a substantial safety record in pregnant women. We now understand the pharmacokinetics of ondansetron at birth based on PK analysis of placental and neonatal blood samples in babies whose mothers' were given ondansetron prophylactically prior to cesarean delivery (Aim 1 of the protocol, Prevention of Neonatal Abstinence Syndrome). In this study, (Aim 2) we will conduct a multi-center, randomized, double blind, and placebo-controlled trial to determine whether ondansetron treatment will reduce the incidence (percentage of infants requiring narcotic drug treatment) or severity (total amount of narcotic drug required, length of hospitalization, symptom severity scores) of NAS in babies born to narcotic-using mothers.

This project tests a very novel approach for preventing an important pregnancy-related complication of narcotic drug abuse. If a brief period of ondansetron administration to the mothers that use narcotic drugs, and to their babies, can prevent or ameliorate the development of narcotic drug withdrawal symptoms in neonates, this would reduce human suffering and the growing societal cost of opiate abuse.

2.0 Protection of Human Subjects

2.1 Risks to Human Subjects

2.1.1 Human Subjects Involvement, Characteristics, and Design

This study will include up to 120 opioid-addicted, otherwise healthy and with no cardiac history of prolongation of the QTc interval, 18-45 years of age, pregnant women ≥ 37 weeks through < 42 weeks gestation and their newborns. Subjects will be recruited from about 5-10 sites around the country with some hospitals joining the study and then dropping out if they are not able to enroll enough subjects. Locally, we are enrolling at two Bay Area hospitals: Lucile Packard Children's Hospital at Stanford and Santa Clara Valley Medical Center. The sites outside of California are: Johns Hopkins Bayview Medical Center in Baltimore, Maryland, the University of Tennessee Health Science Center in Memphis, Tennessee, the University of Louisville in Louisville, Kentucky, and Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

Informed consent will be obtained by either a member of the research team or a member of the participant's medical team during the course of her prenatal care with her obstetrician or at a pre-scheduled visit with the anesthesiologist prior to delivery, or lastly, and the least likely time to get consent may be on admission to labor and delivery, only if time allows true informed consent in that setting. Because this study involves the newborn infant, as well as the mother, consent will be obtained from both parents where fathers are involved and competent to provide consent. After admission to the labor and delivery suite, the mother-infant pair will be randomized to one of two treatment groups (placebo or ondansetron) by the pharmacy. Randomization will be done between all sites to ensure that the first 20 mother-infant pairs enrolled will have an equal number of placebo and active treatment participants. The medical team, the research team, and the participant will be blinded to the treatment assignment (double-blind study). The pharmacy will hold the key to the treatment assignment and will un-blind the study only if deemed medically necessary.

A. Safety Monitoring of Participants:

1. Neonates admitted to Well Baby Nursery:
    a. ECG: The neonate will be stabilized after birth and then will receive a screening 12-lead ECG to rule out QTc Bazett greater than or equal to 480ms. Once the neonate is medically stable and a normal QTc confirmed by the treating physician, the neonate will receive the same 'blinded' study drug (ondansetron or placebo) as his or her mother; this first dose of study drug is to be given between 4-8 hours after delivery. A repeat 12-lead ECG will be done on all neonates following each of the 5 doses of study drug, between 2-5 hours after each dose of study drug. Any neonate that shows significant ECG changes will be excluded from further dosing of study medication but will continue safety follow-up.
        i. If the QTc is prolonged, the neonate will be transferred to the NICU for continuous cardiac monitoring, if the standard of care indicates the neonate should be admitted to NICU; this will be determined on a case-by-case basis at each site. In addition, a blood test to check the potassium, magnesium, calcium, and ionized calcium levels will be done if the clinical team believe it is necessary for the neonates safety; if the levels are abnormal, electrolytes will be normalized using IV or oral supplements as indicated per standard of care.
        ii. All ECGs, from all sites, will be sent to Stanford to be interpreted by a cardiologist, who is not a member of the study team, to confirm the accuracy, and consistency of the initial readings.
    b. Standard of Care for Well Baby Nursery:
        i. Vital Signs: heart rate (HR), respiratory rate (RR), and temperature will be monitored every 4-8 hours depending on the infant's history, and blood pressure at least once per day.
            1. If the HR is less than 80 beats per minute, a rhythm strip or 12-lead ECG is ordered to evaluate the QTc interval, a Neonatal Intensive Care Unit (NICU) physician will assess the neonate and a blood pressure will be obtained.
            2. If the QTc is prolonged, see "ECG" above which discusses the possibility of the neonate being transferred to the NICU for continuous cardiac monitoring if deemed necessary by standard of care
        ii. A member of the study team will visit the Well Baby Nursery at least once per day to ensure the neonate is doing well and that everyone on the clinical team understands the protocol and knows how to contact the principal investigator to answer questions as needed.
        iii. Modified Finnegan Evaluation (Scoring) to be done per standard of care at each institution since they are all similar and have been in place for many years. Each site involved in this study has established guidelines for starting, advancing and weaning treatment for NAS (see attached guidelines for each site). All the data regarding the treatment for NAS will be collected for the study.

2. Neonates Admitted to the NICU after Birth:

a. ECG, Vital Signs, and Pulse Oximetry: the neonate will be stabilized after birth and then will receive a screening 12-lead ECG to rule out QTc Bazett greater than or equal to 480ms. Once the neonate is medically stable and a normal QTc confirmed by the treating physician, the neonate will receive the same study drug (ondansetron or placebo) as his or her mother; this first dose of study drug is to be given between 4-8 hours after delivery. A repeat 12-lead ECG will be done on all neonates following each of the 5 doses of study drug, between 2-5 hours after each dose of study drug. Any neonate that shows significant ECG changes will be excluded from further dosing of study medication but will continue safety follow-up
b. Standard of Care for the NICU:
    i. Blood pressure is measured at least once per shift. Depending on acuity and access, blood pressure will be monitored either continuously (if indwelling line is indicated for clinical care) or every 4-8 hours using non-invasive oscillometry.
    ii. Continuous ECG, heart rate, respiratory rate and oxygen saturation monitoring are done on all NICU patients; the HR, RR, and oxygen saturations are documented in the medical record every 1-4 hours as per standard of care, with vitals documented more frequently in acutely ill infants.
    iii. A member of the study team will visit the NICU at least once per day to ensure the neonate is doing well and that everyone on the clinical team understands the protocol and knows how to contact the principal investigator to answer questions as needed.
    iv. Modified Finnegan Evaluation (Scoring) to be done per standard of care at each institution since they are all similar and have been in place for many years. Each site involved in this study has established guidelines for starting, advancing and weaning treatment for NAS (see attached guidelines for each site). All the data regarding the treatment for NAS will be collected for the study.

Interim Analysis: an interim analysis will be performed after a total of twenty (20) pregnant women and their twenty (20) neonates have been enrolled and dosed with study medication. The analysis will include all the ECG measurements, blood concentration levels for pharmacokinetics (PK) and a reassessment of the PK of ondansetron in neonates, all to be reviewed by the DSMB. The study will only proceed if the DSMB gives their approval. These 20 neonates will be the “First cohort” of neonatal patients. (Note, this was done between April and May 2016)

B. Study Medication Dosing

Adult Pregnant Participant’s Dose: The amount and timing of the dose of ondansetron to be administered to the pregnant participants, who are randomized to the ondansetron group, will be 8 mg (IV) within 4 hours of delivery. Should the participant be undelivered 4 hours following the initial dose of study drug, a second dose will be administered. The study medication will be delivered intravenously to the mother prior to either vaginal or cesarean delivery. Exception: if the pregnant participant does not want to receive any study medication prior to delivery because she is not experiencing nausea, she may still continue to be a part of the study and her neonate will be assigned to the study medication she would have been randomized to receive. This allows for an adult patient to not be given the study medication

(ondansetron or placebo) if they feel they do not need it. The neonate's participation will continue as planned.

Neonatal Participant's Dose: The neonates who are born to the mothers, who are randomized to receive ondansetron, will have an initial oral dose of ondansetron 0.07 mg/kg given between 4-8 hours after delivery. The subsequent doses of ondansetron will be 0.07 mg/kg orally every 24 hours for up to 5 doses maximum.

The timing and volume of placebo administration for the 50% of subjects in the placebo group will mimic that of the 50% of subjects in the ondansetron group. Placebo will consist of either normal saline for IV administration or inactive oral syrup for oral administration.

For those neonates who require an intravenous catheter for any other medical reason, these neonates will receive an ondansetron dose of 0.04 mg/kg IV every 24 hours for up to 5 doses maximum.

C. Study Procedures

Adult Pregnant Participant's Procedures:

1. Maternal blood for ondansetron concentration (PK) will be collected within 30 minutes of delivery (either pre- or post-delivery).

2. Maternal urine will be collected for toxicology analysis prior to delivery to identify possible polysubstance abuse (polysubstance use is not an exclusion criteria)

3. Once delivery is complete, the mother's participation will consist mainly of answering questions about her own medication use and the baby's feeding habits over the remainder of the study while the neonate participates in the study.

Neonatal Participant's Procedures:

1. The Modified Finnegan scoring system will be used to evaluate neonates for symptoms of NAS at each site involved in the study and is considered standard-of-care for babies who are at risk for NAS. Treatment with the study medication will continue for a maximum of five days (starting within approximately 4-8 hours after birth).

2. Treatment of NAS: morphine will be the first treatment choice before other treatment medication choices (opioid or non-opioid) for NAS symptoms. This is the standard-of-care at all participating sites. Each site involved has established guidelines for starting, advancing and weaning treatment for NAS. Any medication used to treat the symptoms of NAS will be noted as to name, dose, route, reason for dosage (Finnegan score or other reason) and time of administration. If the neonate develops nausea and clinical treatment of the nausea would include ondansetron then an alternate antiemetic should be considered. The infant may already have a full therapeutic level of ondansetron and additional dosage will not help treat the nausea. Ondansetron is not strictly contraindicated by this protocol as some neonates will have received placebo. For those infants that have been randomized to ondansetron, an additional dose of ondansetron will not be harmful.

3. 12-Lead ECG: all neonates, whether they are cared for in Well Baby Nursery or the NICU, will have a screening 12-lead ECG prior to their first dose of study drug and a follow-up 12-lead ECG within 2- 5 hours after each dose of study drug.

4. Umbilical cord blood (venous) will be collected at delivery and evaluated for ondansetron and ondansetron metabolite concentration. The standard of care at most hospitals is to discard the umbilical cord in the hospital biological waste system unless the parents have asked for it to be saved. We will only take these cord samples if the mother agrees to let us have them.

5. Blood Samples: between one (1) and nine (9) 0.1 mL blood samples (about 1-3 drops) will be collected from the neonate after birth to measure ondansetron and metabolite concentrations. These samples will be collected during clinically indicated blood sampling whenever possible to prevent additional trauma to the infant. When and if an intravenous cannula is inserted for administration of other treatments and then the study drug, a blood sample may be obtained during the insertion of this cannula, if possible, to avoid a heel stick for the PK blood draw done prior to starting IV dosing of study drug. If there are no clinically indicated blood draws ordered for a neonate in the first 12 hours of life, it may be necessary for one or two of these research PK samples to be drawn separately from clinically indicated sampling. For example, if there are no clinically indicated labs that need to be done prior to the first dose of study drug, then the first PK sample of blood would be done for research only, if the mother agrees to a heel stick. The second PK sample is scheduled to be drawn after the first dose of study drug but before the infant is 12 hours old and that would be an extra heel stick if there are no clinically ordered labs during this time period. During the following days of treatment, additional 0.1 ml of blood will be obtained when clinically indicated blood sampling occurs up to a grand total of 9 times during the study. Times will be noted to the nearest minute for all blood samples.

6. Follow-up calls/visits: a research team member will call the mother of the baby once they have been discharged home, if the baby is discharged prior to Day 15 of their life. We want to follow up on the babies and learn how they are doing and make sure they are not going into “Delayed” NAS. For babies who are discharged early it is more likely they could go into delayed NAS and that is why we plan to call the mothers daily, for up to 10 days after the baby takes their last dose of study medication, to ask about their baby’s status. We are interested in how the baby is feeding, are they breast or bottle feeding the baby, what is the baby’s mood (crying excessively, fussy, agitated), sleeps for how many hours after feeding, sneezing a lot, sweating, vomiting, gaining weight, loose stools or watery stools, etc. We also need to ask the mother all the medications she is taking, if she is breastfeeding her baby, since we know these medications will enter the baby’s system through the breast milk. If a baby is not discharged before day 15 of their life, the research team member will visit the baby in the hospital daily, for 10 days after their last dose of study drug, to check on the status of the baby from the clinical team caring for the baby. If the mother is home while the baby remains hospitalized, the research team member will also call the mother on a daily basis to maintain contact and to ask the mother all the medications she is taking if she is breastfeeding her baby (we know these medications may enter the baby’s system through the breast milk).

7. The final follow-up call (or visit if the baby is still in the hospital) will occur approximately 30 days after the baby's last dose of study medication; this call (or visit) will be to determine if any previously reported adverse events have resolved and/or if any new adverse events have occurred since the last follow-up call or visit.

The primary endpoint will be the incidence of NAS in enrolled neonates and will be measured by the need for pharmacologic treatment for the symptoms of NAS (Morphine). The secondary endpoint of the severity of NAS will be measured by the length of the hospitalization (birth to discharge), the total dose of narcotic required to treat the symptoms of NAS, and the need to include barbiturates in the treatment of symptoms of NAS.

2.1.2 Inclusion/Exclusion

Criteria

Subjects	Inclusion Criteria	Exclusion Criteria
Maternal/Paternal	Women of reproductive age (18-45 years old, inclusive) and their fetuses/neonates. Daily opioid use for at least 3 weeks prior to delivery Gestational age of ≥- 37 weeks to < 42 weeks at delivery. Competent mother willing to sign the informed consent for herself and both parents competent and willing to sign consent/permission for their neonate.	Any condition that, in the opinion of the investigator, would compromise the health of the participant (both mother and fetus) or the integrity of the data. Known allergy to the study medication. Screening 12-lead ECG, if done, showing prolonged QTc will stop the mother from receiving any study drug but her neonate can still be included in the study. Maternal ingestion or administration of ondansetron within 24 hours prior to delivery, for reasons other than study purposes, will exclude the mother and neonate.
Neonatal	Participating mother Maternal (and paternal if	QTcB greater than or equal to 480ms on any 12-lead

	present and competent) consent	ECG post delivery will stop the dosing of the study drug, but safety follow up will be done including blood samples & 12-lead ECG(s) if the mother or baby received at least one dose of study drug.

This study will include special classes of participants: pregnant women and their newborns. The focus of this study is specific to these sensitive populations of pregnant women and neonates and as such warrants their inclusion. We feel that, in balance, the potential for significant benefit to the neonatal population in this study and in future patients outweighs the risks (section 5.0 *Potential Risks* below).

2.2 Collaborating Sites

This study will occur at the following hospital sites.
1. Lucile Packard Children's Hospital/ Stanford University Affiliate (Stanford, California)
2. Santa Clara Valley Medical Center/ Stanford University Affiliate (San Jose, California)
3. Johns Hopkins Bayview Medical Center/ Johns Hopkins University Affiliate (Baltimore, Maryland).
4. University of Tennessee Health Science Center/ University of Tennessee Affiliate (Memphis, Tennessee)
5. Kosair Charities Pediatric Clinical Research Unit / University of Louisville Affiliate (Louisville, Kentucky)
6. Thomas Jefferson University Hospital / Thomas Jefferson University Affiliate (Philadelphia, Pennsylvania)

These medical centers have collaborated multiple times in ongoing, prospective, maternal-fetal studies (*43*). Stanford University will act as the coordinating center, managing all aspects of the study including grant management, enrollment oversight, protocol compliance, PK specimen processing, subcontracting, and safety monitoring. All four sites will enroll and treat participants and be responsible for the safety of participants and integrity and safety of data at their respective sites.

3.0 Study Team

We have assembled an outstanding team of clinicians and scientists

Role/ Location	People
Clinical Coordinator/PI Lucile Packard Children's Hospital	David Drover, MD
Clinical Team 1. Lucile Packard Children's Hospital (LPCH, site 1) 2. Santa Clara Valley	Deirdre Lyell, MD; Ronald S. Cohen, MD; Brendan Carvalho, MBBCh, FRCA, MDCH; Carol Cohane, RN Balaji Govindaswami, MD; Priya Jegatheesan, MD

Medical Center (SCVMC, site 2)	
3. Johns Hopkins Bayview Medical Center (JHBMC, site 5)	Lauren M. Jansson, MD
4. University of Tennessee Health Science Center (UTHSC, site 6)	Ramasubbareddy Dhanireddy, MD
5. University of Louisville (U of L, site 8)	Lori A. Devlin, D.O.
6. Thomas Jefferson University Hospital (TJU, site 7)	Walter K. Kraft, MD; Susan Adeniyi-Jones, MD
Science Team Lead/co-PI	David Drover, MD
Clinical research RN	Carol Cohane, RN
Statistician	Ming Zheng, PhD
Mass Spectroscopy	Manhong Wu, PhD
Clinical Pharmacology	Robert Ward, MD

4.0 Sources of Materials

4.1 Maternal and Neonatal Tissue

Maternal Tissue: one maternal blood sample for ondansetron levels will be collected within 30 minutes of delivery (pre- or post-delivery) but as close to time of birth as possible. Time of this blood sample will be recorded as accurately as possible and related to the time of birth. A maternal urine sample will be obtained prior to delivery for a toxicology screen to determine possible polysubstance abuse.

Neonatal tissue: umbilical cord blood (venous) will be collected at delivery and evaluated for ondansetron and metabolite concentrations. Between one and nine 0.1 mL blood samples (1-3drops) will be collected from the neonate to measure ondansetron and metabolite concentrations after birth. Most of these samples will be collected during clinically indicated

blood sampling to prevent additional trauma to the infant. (See Section 2.1.1. under section C. Study Procedures, #4, for details on blood draws)

4.2 Maternal data

1. Age, 2. Weight, 3. Height, 4. Race & Ethnicity, 5. Drug(s) of abuse used, and dose, frequency and duration of use, 6. Name, 7. Other substance abuse, 8. Tobacco use and amount/day, 9. Medications used during pregnancy that might induce or inhibit metabolism of ondansetron or change QT (e.g., CYP 3A4, 2D6, barbiturates, fluconazole, erythromycin, etc.), 10. Maternal co-morbidities, 11. Plan to breast feed, and level of success as measured by number and length of feedings per day, number of formula feedings per day, 12. Type of labor/C-section analgesia, 13. Opioid and other drug use during breast feeding. 14. Gravida 15. Para, 16. Date of Birth, 17. PK blood results for ondansetron, 18. Urine drug screen results 19. Medical record number.20. Name & contact number of their baby's pediatrician and/or other healthcare provider, such as public health nurse. 20. Results of 12-lead ECG, if done.

4.3 Neonatal data

1. Gestational age, 2. Mode of delivery, 3. Birth weight, 4. Birth Length (height), 5. Neonatal co-morbidities, 6. Duration of hospital stay (birth to discharge), 7. Need for medical treatment of NAS, 8. Time from birth to initial pharmacological treatment of NAS, 9. Need for barbiturate treatment for NAS, 10. Duration of medical treatment of NAS, 11. Weight change during hospitalization, 12. Gender, 13. Modified Finnegan scores, 14. All 12-lead ECG results, 15. Frequency and duration of breast/bottle feeding in hospital and home after discharge, 16. Apgar 1min, Apgar 5 min 17. All medications used to treat NAS (drug name, dosage, route, reason for dosing, time & date), 18. pharmacokinetic blood results for ondansetron, 19. Date of birth, 20. Medical record number.

Data Security
Study team members at all sites will have access to the identifiable protected health information (PHI) of participants. During the data-collection phase of this study, all identifiable data will be kept in a locked environment. All electronic data will be encrypted and kept on a password-protected computer. A REDCap database will be designed and maintained by the study team for the compilation of all study data. This database meets all regulatory standards for safe and confidential storage and management of human subject research data. At the earliest possible time, after complete analysis and confirmation of accuracy of the data collected, all data will be de-identified.
A unique study number will be assigned to each participant. The code to link this number to PHI will be encrypted and kept in a password-protected computer. Tissue specimens for ondansetron levels will be labeled with this coded study number only and will not include any information that would link the sample to the participant. The urine toxicology screens will be analyzed in the respective hospital laboratories.
Due to the sensitive nature of the data collected and to protect the rights of the study participants, a Certificate of Confidentiality was obtained from the NIH on August 21, 2013.

5.0 Potential Risks

Potential Risks
Ondansetron

Potential Risks
To Mother Well-studied in adults and considered safe Routinely given to pregnant women in first trimester for hyperemesis gravidarum and during labor as antiemetic Routine doses used in this protocol minimize risks to the mother
To Fetus Classified as pregnancy class B (not shown to cause teratogenicity in animal studies and not well-studied in humans) Commonly used clinically in labor and delivery to treat maternal nausea, thus exposing the fetus transplacentally Considered to have minimal risk to the fetus
To Neonate Not well-studied in this age group Used clinically to treat postoperative nausea in infants and young children and considered to carry minimal risk One double-blinded, randomized, controlled trial compared ondansetron to placebo for preventing postoperative emesis in 1-24 month olds {#22}. No differences were found in number or pattern of adverse events between groups
Delayed onset of NAS
To Mother Not applicable
To Fetus Onset of NAS symptoms may be delayed as a result of ondansetron treatment Given the prolonged effects of methadone, the late-onset risk may be particularly relevant to patients on methadone
To Neonate If neonates do not demonstrate symptoms of NAS prior to discharge from the hospital; parents will be instructed to closely observe for symptoms when home and told to either call their baby's doctor or take their baby to their pediatrician if the baby is showing signs of NAS
Phlebotomy
To Mother Minimal risk Approximately 5 cc (one teaspoon) maximum of blood will be drawn from the mother by needle stick or she can have a finger stick if the site uses the filter paper to obtain dried blood spots. Rare side effect is hematoma and/or infection
To Fetus Not applicable
To Neonate Study drug will be administered to the neonate either orally or via standardized intravenous infusion (IV) technique for this population, posing no additional risk
Heel Stick
To Mother Not applicable
To Fetus Not applicable
To Neonate Do heel stick to collect 1-3 drops of blood at least twice after delivery only if blood not collected for clinical reasons in the first 12 hours after birth Minimal risk of hematoma or infection
Electrocardiogram
To Mother May have a screening ECG if she has a history of prolongation of QTc or the investigator believes there may be a cardiac history of arrhythmia. Small risk of skin irritation from the stickers used for the ECG
To Fetus Not applicable
To Neonate A screening ECG will be done shortly after birth (must be done & interpreted before study drug administration). Repeat ECG done after each dose of study medication. Small risk of skin irritation from the stickers used for the ECG.
Urine toxicology screen
To Mother Done for all study participants Has legal and social implications Routinely done on pregnant woman with known history of substance abuse Risks not significantly different from those not participating in study
Confidentiality
All Subjects Conduct enrollment in private rooms away from public workspaces Only protocol- trained and HIPAA-trained personnel will enroll patients, assuring confidentiality and security of patient

Potential Risks
information Upon signed consent, mother-infant pairs will be randomized by designated clinical pharmacist, based on computer-generated randomization scheme The names and medical records of mother-infant pairs will be kept in pharmacy log, kept in locked files accessible only to the designated clinical pharmacist The clinical pharmacist assigns mother-infant pair a coded number used for data collection For statistical analysis, at study conclusion clinical pharmacist gives primary study investigators the logs that link coded numbers with study medication. These logs will be kept separate from the final outcome database. For clarification, the clinical pharmacist will assign the patient a study number to be used for randomization and for clinical data collection after patient enrollment After study completion and one year after manuscript publication, destroy records linking participants' identities to study ID numbers Do not reveal participants' identities in any publications Keep consent forms in locked files and maintain confidentiality of all study-related records in accordance with State and Federal laws Obtain Certificate of Confidentiality from NIH to protect identifiable research information from forced disclosure Certificate application will list Stanford University (the lead institution) and all sub-award sites to protect all participants from forced data disclosure
To Fetus Not applicable
To Neonate Not applicable

6.0 Adequacy of Protection against Risks

6.1 Recruitment and Informed Consent

We will recruit patients from the Obstetric clinics affiliated with each study site as early as possible in the woman's pregnancy. Many of these pregnant women have what is considered 'high risk' pregnancy due to their own narcotic-dependence. These women will most likely be seen by the Anesthesia Department in a scheduled visit prior to their due date to allow the anesthesiologist time to evaluate the mother's health and anesthetic needs for her delivery; during this visit the women will be told about the study and asked if a study team member can explain the study to them in detail. The least likely method of recruitment will be a patient who presents to Labor and Delivery to deliver their baby and who has not been seen in advance by the study team. Among this group, we will not approach or enroll women who are in active labor; we may approach women who are not yet in labor or who are in very early labor (as occurs with many other Labor and Delivery studies), allowing them sufficient time to consider study participation and allowing sufficient time for us to activate all study related events. All women invited to join this study will be advised that regardless of their decision to participate, they will receive the full spectrum of standard treatment on Labor and Delivery and postpartum.

Staff at local methadone maintenance clinics will also inform their pregnant clients about the study and be given an IRB approved flyer with the name and telephone number of a study team member to call; or they may prefer a study team member to call them, and if they give the clinic their verbal permission, then and only then, a study team member will call them to explain the study.

Written information about the study, including the purpose of the study, the nature of the subject's participation, and the potential benefits of participation will be offered. All necessary human subjects' reviews and approvals are obtained prior to implementation of any study related procedures at any recruitment site.

When a potential participant indicates an interest in participating in the study, a member of the study team will describe the study in greater detail, ensuring mental competence and full understanding of the implications of participation. A signed, informed consent will be obtained after the participant is given time to ask questions about the study.
Once delivered, the neonate will become the participant. Given this, a "Parental Permission" consent will be obtained from both the father and the mother at the time of maternal enrollment. We understand that we do not have to obtain consent of the father if he is unable to consent because of unavailability, incompetence, or a temporary incapacity, or if the pregnancy resulted from rape or incest. Each individual (the mother and father if present and competent to provide consent) providing consent for participation in this study will be fully informed regarding the reasonable foreseeable impact of the research on the neonate.

6.2 Protection against Risks

All subjects in the study will be cared for by the same team of physicians and nurses, both on

the Labor and Delivery unit and in the neonatal intensive care unit, just as patients would be cared for if they were not part of the study. All teams will be led by appropriately trained attending physicians, both obstetricians and pediatricians. Of note, mothers, fetuses and neonates will receive the standard of care for all medical problems that arise. This includes administration of narcotic medications for signs or symptoms of neonatal narcotic withdrawal according to each hospital's established protocol; narcotic administration is dependent upon the Modified Finnegan score and clinical assessment of the clinical team. Thus, neonates in both the placebo and the ondansetron group will receive the standard of care for neonatal abstinence syndrome.

All participants will be closely observed for adverse events. If a study drug related serious adverse event is noted, the study drug will be discontinued and the adverse event reported to the principal investigator, the IRB and the Data Safety Monitoring Board (DSMB). Detailed information regarding data safety and monitoring will be described in section 9.0 *Data and Safety Monitoring Plan*.

Due to the nature of this study, this research involves vulnerable populations, including pregnant women, fetuses, and children (neonates). We feel the risk to both the mother and neonate are minimal, and the least possible to achieve the goals of this project, and that the potential benefits to narcotic exposed fetuses and neonates greatly outweigh the risks. Specific information regarding the risks follows.

Specific risks include the following:

Specific Risks
Ondansetron
To Mother Maternal risk is minimal, as medication is commonly used in setting and population
To Fetus Risk of ondansetron exposure is same as currently occurs during standard of care treatment of pregnant women at risk for nausea and emesis
To Neonate Risk is no greater than placebo risk To minimize risk, screen for QT prolongation and give dose (determined in Aim 1) to reach blood level predicted to have desired clinical effect Dose will be within dose limits studied in slightly older infants (less than 0.15 mg/hr in 12hours) Duration of exposure will be minimized by stopping study drug after a maximum of five days of study drug treatment, Will be discontinued if related adverse events occur If QTc interval abnormalities occur or a neonate has QTcB greater than or equal to 480 ms, the neonate's study drug will be stopped and no further dosing will occur; follow up 'safety' EKGs will be done until the QTc has returned to 479ms or less, if possible. All neonates will have a screening ECG prior to their first dose of study medication & an ECG after each dose for a maximum of 6 ECGs in 5 days.
Delayed onset of NAS
To Mother Not applicable
To Fetus Risk will be managed by educating the parents about the NAS symptoms Provide parents with contact information for both their clinical caregivers and the research team Ask parents to report delayed onset to both groups Appropriate medical care will be provided Parents may receive a maximum of 10 daily follow-up telephone calls if the baby is discharged before Day 15 of life; the calls are being done to review continuation or recurrence of NAS symptoms and the occurrence of other adverse events. The research staff will call daily, through a maximum of 10 days after the last dose of study drug. If the baby is still in the hospital through Day 15 of life, this information will be gathered by the research staff visiting the neonate in the hospital. The final follow-up phone call to the parents will occur approximately 30 days after the baby's last dose of study medication to check for any occurrence of new adverse events and to inquire about the resolution of any previously reported adverse events.
To Neonate Not applicable
Phlebotomy
To Mother Minimize risks of hematoma and infection by following all hospital guidelines including using aseptic technique and applying pressure to site after sample collection Only qualified personnel may collect blood samples for analysis
To Fetus Not applicable
To Neonate Minimize risks of hematoma and infection by following all hospital guidelines including using aseptic technique and applying pressure to site after sample collection Only qualified personnel may collect blood samples for analysis
Heel Stick
To Mother Not applicable
To Fetus Not applicable
To Neonate Minimize risks of hematoma and infection by following all hospital guidelines including using aseptic technique and applying pressure to site after sample collection Only qualified personnel may collect blood samples for analysis
Electrocardiogram
To Mother Not applicable
To Fetus Not applicable
To Neonate Minimize skin irritation with ECG pads designed for neonates, and observe sites for signs of irritation and inflammation
Urine toxicology screen
To Mother Reduce social and legal risks by following all HIPAA and human subject research regulations

Specific Risks
Prior to study enrollment, obtain a Certificate of Confidentiality from NIH to protect identifiable research information from forced disclosure
To Fetus Not applicable
To Neonate Not applicable

6.3 Protection of Confidentiality

We will take extensive precautions to maintain participant confidentiality throughout the study. The enrollment will be conducted in private rooms away from public workspaces. Only protocol-trained and HIPAA-trained personnel will enroll patients. Upon signed consent, mother and infant pairs will be randomized by the pharmacy based on a computer-generated randomization scheme. Only the pharmacy log will have the name and medical record of the mother-infant pairs. The log will be kept in locked files in the pharmacy and will be accessible only to the clinical pharmacist designated by the coordinators. The pharmacy will then assign the patient a coded number that will be used for data collection. At the conclusion of the study, the pharmacy will provide the primary study investigators the logs linking the numbers with the study medication for statistical analysis of the data. The logs linking the names and medical record numbers will be kept separately from the final outcome database.
For clarification, the pharmacy will assign the patient a study number used for randomization and for clinical data collection after patient enrollment.
All study personnel are HIPAA trained and certified and appreciate the importance of confidentiality and the security of personal information.
Participants' identities will not be revealed in any publication that may result from the proposed study. Consent forms will be kept in locked files, and the confidentiality of all study-related records will be maintained in accordance with State and Federal laws.

A Certificate of Confidentiality was obtained from the NIH on August 21, 2013, to protect the identifiable research information from forced disclosure. The application will include Stanford University (the lead institution) and all sub-award sites listed in this application. It is of utmost importance to protect all participants from forced disclosure of this data.
In the event of study related adverse events, Dr. Drover, in his role as Clinical Medical Coordinator and Primary Investigator in this study, will provide direct care, or facilitate appropriate referrals to ensure successful resolution of the AE. A Data Safety Monitoring Board will be established, and will be described in greater detail in section 9.0.

7.0 Potential Benefits of the Proposed Research to the Subjects and Others

Mother-infant pairs randomized to the ondansetron arm may benefit from the following: decreased need for medical intervention for the neonate, decreased amounts of post-natal narcotic given to the neonate, decreased neonatal weight loss, and decreased length of neonatal hospital stay. There is no direct benefit to mother-infant pairs randomized to placebo. However, physician interest in mothers and neonates with narcotic exposure may make this population of women feel better understood and better cared for by the medical community. This may improve the patient's satisfaction with her care.
Because of ondansetron's safety record, the severe nature of NAS, and the significant animal and human pre-clinical data suggesting that ondansetron reduces or abolishes opioid withdrawal, we believe that the benefits of this trial far outweigh the risks.

8.0 Importance of the Knowledge to be Gained

The long-term research goal is to develop safe treatments that decrease the extent and severity of Neonatal Abstinence Syndrome for infants born to mothers using narcotics during pregnancy. We believe there will be significant benefit from improvement in initial neonatal disability and decrease in the length of the hospital stay for infants affected by neonatal abstinence syndrome due to maternal narcotic use. We believe the benefits to be obtained outweigh the minimal risks of involvement in this study.

Well-controlled research evaluating medications during pregnancy and the neonatal period is needed, so that patients can receive the best care possible from their providers. Providing pregnant women and their neonates with a safe and effective way to decrease withdrawal symptoms in the neonates will potentially benefit thousands of women and their children. In addition, if the duration of neonatal symptoms is limited, the reduction in neonatal hospital stay could save millions of dollars.

The knowledge gained from this study may also impact treatment in the following ways:

Established treatment practices may be altered in response to the information gained from this study.

Experience from this study and developed infrastructure will allow for the evaluation of other medications within this research team to advance the treatment of drug-dependent pregnant women and their drug-exposed children.

Increased information about the pharmacokinetic changes of ondansetron in pregnant women may be extrapolated to other medications with similar pathways of clearance used in pregnant women.

From examination of maternal transfer of ondansetron to the neonate by measuring uterine cord blood and neonatal concentrations of drug, we will better understand the transfer of drug to the neonate form the mother.

From examination of metabolite profiles of ondansetron in the neonate and comparison of umbilical venous and arterial concentrations, we anticipate being able to estimate the hepatic enzyme activity of the fetus and neonate.

9.0 Data and Safety Monitoring Plan

A Data Safety Monitoring Board (DSMB) will be established to ensure the safety and welfare of the subjects enrolled, to ensure the quality of the data, and to make intermittent recommendations whether to continue, modify or stop the trial. The members of the DSMB will be appointed by and report to Dr. David Drover. The Board members will be independent of the study group. Members will possess expertise in obstetrics, neonatology, addiction, biostatistics, and medical ethics. The Board will also include a public ombudsman, a member from outside of the investigators' institution, and a non-voting secretary, who will keep a written record of every meeting.

DSMB members will disclose in writing to the IRBs of all study institutions any potential conflicts of interest, actual or implied by appearance. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data.

An initial DSMB meeting to discuss the protocol and to establish specific guidelines for monitoring the study will occur before the trial is started. Once the trial commences, interim reports will be sent to the DSMB before each scheduled meeting. The content of the reports will be determined by the DSMB. During the course of the study, any changes to the trial

and/or reporting activities will be made as required by NIH and/or the DSMB.
The DSMB will have discretion to un-blind any results or conduct any inquiry needed to ensure the safety and efficacy of the trial at the request of the DSMB chair. The secretary will maintain a written record of its meetings. Meetings will be scheduled every six months; expedited meetings will be scheduled to review any serious adverse events or adverse events judged by the investigators to be study-drug-related.
The meetings will be divided into three sessions: open, closed, and executive. During the open session, Dr. David Drover will present relevant information about the trial including the following: 1) number of subjects enrolled, 2) problems with data accrual or follow up, 3) baseline demographic data, 4) compliance issues, 5) frequency of adverse events, 6) documentation of efficacy endpoints, 7) data quality issues, 8) flow of forms, and 9) data based protocol modification issues. Following the open session, a closed session will be held. During the closed session, the DSMB chair will conduct a review of all issues and put each issue to a vote. The discussion will focus on treatment safety, efficacy of data, and whether the primary study question has been answered in order to determine when the study data may be released or if an interim analysis is necessary. Following the closed session, an executive meeting may be held to discuss any unmasked analysis of the trial and any sensitive issues surrounding the trial. DSMB recommendations will be made in writing by the DSMB chair to Dr. Drover.
The secretary will prepare meeting minutes for inclusion in the DSMB report. The report prepared by the DSMB will outline and summarize all discussions during the open and closed sessions of the meeting. The draft report will be reviewed by all Board members prior to issuance of the final report. DSMB recommendations will then be forwarded to the NIH program officer and to the IRB at each study site.
We are most concerned with the risk of ondansetron exposure to the neonate, although we do not expect significant adverse events attributable to ondansetron compared to placebo (see description of known risk in section 5.0 *Potential Risks*). The Common Rule defines adverse events (AEs) as unanticipated problems. We will use this definition in our reporting and in addition include the potential risks defined in this application. Minor events would include hematoma at phlebotomy site, neonatal rash at electrocardiogram lead sites, or minor maternal side effects mentioned above in section 5.0 *Potential Risks*. We will use the FDA definition of serious adverse events (SAEs) in our reporting. Members of the study team at each site will report AEs and SAEs to Dr. David Drover and to their local IRB as required at each site. SAEs will be reported within 24 hours of each site's awareness of that event. Within ten working days after receiving a report, Dr. David Drover will report related AEs and SAEs to the following: Stanford's IRB as the Lead Site IRB, the Data Safety Monitoring Board (DSMB), and the NIH funding institute. He will then follow-up with a written report within 10 working days. The DSMB will determine appropriate action following review of any reported event, and this will be communicated to all study sites, the IRB and NIH funding institute.
Each party (Stanford University as the lead site, and all sub-award sites mentioned in this application) will indemnify for its own negligent acts or omissions. Indemnification will be addressed in the contracts with the sub-award sites, but the specific language is not predetermined, and is therefore not available. The study medication will be subject to normal market warranties for proper manufacturing and labeling.
Dr. Drover has applied for an Investigational New Drug (IND) application for ondansetron in neonates to prevent neonatal abstinence syndrome. IND #112007. The application was accepted by the FDA on May 23, 2014, when the Full Clinical Hold was removed for this

protocol. We are proposing a novel clinical investigation that will evaluate the efficacy of a drug for this novel indication. Although Dr. Drover has applied for this IND for a new indication of ondansetron, we are not using this data to obtain a new use indication or a label change for this drug from the FDA.

10. Clinical Trials.gov Requirements

This project includes an applicable clinical trial that required registration in ClinicalTrials.gov. The CT.gov number is: **NCT01965704.** This registration was accomplished prior to enrollment of any study participant.

11. Inclusion of Women and Minorities

All adult participants in the study will be female. Males will be excluded because the research question is only relevant to the female gender. Neonates may be either male or female, and we expect an essentially even neonatal gender distribution. No racial or ethnic groups will be excluded from participating in this study, and we expect participants to represent the ethnic mix of San Francisco, San Mateo, and Santa Clara counties.
The Targeted/Planned Enrollment Table immediately following the Human Subjects Section gives a breakdown of anticipated participants by ethnicity, race, and gender.

12. Targeted/Planned Enrollment Tables

Targeted/Planned Enrollment Table 1

Total Planned Enrollment : **120 Neonates**

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	8	8	16
Not Hispanic or Latino	52	52	104
Ethnic Category: Total of All Subjects *	60	60	120
Racial Categories			
American Indian/Alaska Native	3	3	6
Asian	16	16	32
Native Hawaiian or Other Pacific Islander	4	4	8
Black or African American	3	3	6
White	34	34	68
Racial Categories: Total of All Subjects *	60	60	120

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

Targeted/Planned Enrollment Table 2

Total Planned Enrollment: **Up to 120 maternal subjects**

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	16	0	16
Not Hispanic or Latino	104	0	104
Ethnic Category: Total of All Subjects *	120	0	120
Racial Categories			
American Indian/Alaska Native	6	0	6
Asian	32	0	32
Native Hawaiian or Other Pacific Islander	8	0	8
Black or African American	6	0	6
White	68	0	68
Racial Categories: Total of All Subjects *	120	0	120

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subiects.”

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Appendix

Pharmacy Instructions for NICHD Protocol

Aim 2: Prevention of Neonatal Abstinence Syndrome (NAS2)

Double-blind study therefore only the pharmacist will know which study medication (ondansetron or placebo) the pregnant woman will receive; the neonate is assigned the same study medication their mother received. (Only one randomization number for the maternal/neonate pair).

Pregnant women randomized to IV ondansetron:

- The IV dose of ondansetron will always be 8mg per dose (ondansetron concentration is 2mg/mL, thus 4 mL = 8mg)
- The **woman's dose may be repeated one time** if she does not deliver her baby within 4 hours of the first dose of ondansetron.

Pregnant women randomized to IV placebo:

- **IV placebo** is prepared to "**mimic the volume"** of the 8mg dose of ondansetron.
- Prepare **IV placebo** with **normal saline 4 mL** (0.9% Sodium Chloride injection).
- The **pregnant woman's dose may be repeated one time** if she does not deliver her baby within 4 hours of the first dose of placebo.

Neonates assigned to ondansetron:

- Dose is based on **birth weight**.
- **Oral dose is 0.07 mg/kg every 24 hours** starting the day of birth, between 4-8 hours of life, and continuing for a maximum of 5 doses of study medication.
- Concentration of oral ondansetron 0.8 mg/mL
- **IV dose is 0.04 mg/kg every 24 hours** starting the day of birth, between 4-8 hours of life, and continuing for a maximum of 5 doses of study medication.
- The route of dosing may start with oral or IV doses or may be switched from oral to IV dosing at any time if the NICU/Research teams believe it is best for the baby.
- Concentration of IV ondansetron is 2mg/mL

Neonates assigned to placebo:

- Dose is based on the **birth weight.**
- **Simple Syrup** will be used for **oral placebo** doses. (Manufacturer: Humco. NDC # 0395-2661-16; 16 oz bottle)
- **Oral placebo** must **"mimic the volume"** of a dose of ondansetron, as if the baby had been assigned to oral ondansetron 0.07 mg/kg.
- **Normal saline** (0.9% Sodium Chloride injection) will be used for **IV placebo** doses.
- **IV Placebo** must "mimic the volume" of a dose of ondansetron, as if the baby had been assigned to IV ondansetron 0.04 mg/kg per dose.