"Can Ondansetron Prevent Neonatal Abstinence Syndrome (NAS) in Babies Born to Narcotic-dependent Women (AIM2NAS)"

Parental Permission Informed Consent

NCT# 01965704

Date of IRB approval of the ICF: April 26, 2016

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Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to allow your baby to participate in a research study of the Prevention of Neonatal Abstinence Syndrome (NAS) because we believe your baby may be at risk to develop NAS after he/she is born. NAS is a combination of symptoms that develop in a baby who is born to a mother who is dependent on (using) narcotics every day (examples of narcotics: methadone, morphine, codeine, oxycodone, vicodin). The use of and addiction to narcotic medications has become the most rapidly increasing drug problem in the U.S.A., which has consequences for the pregnant mothers and their babies. NAS develops in 42-94% (42 to 94 out of 100) of the babies born to these narcotic-dependent women. There are no treatments to prevent this severe syndrome, which can result in a long hospital stay and treatment in the neonatal intensive care unit (NICU) for the baby. A 'neonate' is a baby from birth through 27 days old; 'abstinence' is the stopping of or absence of a drug that has been taken routinely, such as taking a baby's access to narcotic medication away due to delivery of the baby; 'syndrome' is defined as a group of symptoms, such as: sweating, excessive crying or high-pitched crying, irritability, poor feeding, diarrhea, vomiting, and poor weight gain.

We hope to learn if we can prevent or lessen Neonatal Abstinence Syndrome in babies by giving the narcotic-dependent mothers a dose of intravenous (IV) ondansetron prior to delivery, followed by giving their babies up to 5 days of oral (PO) ondansetron. Ondansetron is a drug commonly used to prevent nausea after surgery and has an excellent safety record in pregnant women who use it to help reduce or prevent nausea in the first 3-months of their pregnancy. Based upon a genetic discovery, we demonstrated that administration of ondansetron prevented the symptoms of narcotic drug withdrawal (abstinence) in experimental studies in mice and in humans. If we can reduce or prevent the development of narcotic drug withdrawal symptoms in newborn babies, in other words, prevent NAS, this would decrease the suffering of these babies.

Currently there is no standard drug used to "prevent" NAS, therefore, babies born to narcotic-dependent mothers are allowed to show signs and symptoms of NAS first and then they are treated with a narcotic (morphine is the standard of care at Stanford & the hospitals involved in this study) given either intravenously (IV) or orally (PO) to help lessen the suffering of the babies.

This project was designed as a randomized, double-blinded, placebo controlled study.

1. Randomized: there will be a computer–generated list to tell the pharmacist which study medication to prepare for each subject. The medical team physician cannot make this decision.
2. Double-blinded: the medical team involved in the treatment of the mother and baby, the study team members, and the mothers themselves will be blinded (will not know) which one of the two treatments they will receive. Only the study pharmacist will know which treatment is received.
3. Placebo controlled: one half (45 of the 90) of the narcotic-dependent mothers and babies will receive placebo study medication (inactive drug made from inactive sugar water if given orally or salt water if given through a vein) and the other half (45 of 90) of the mothers and babies will receive active study medication, oral ondansetron, or IV ondansetron if needed.

Your baby was selected as a possible participant in this study because you are pregnant, currently dependent on a narcotic medication (daily narcotic use for at least 3 weeks prior to delivery), in generally good health, 18 through 45 years old, having one baby, and planning to deliver at Stanford Hospital when the gestational age of your fetus is between 37 to 42 weeks.

If you decide to stop your baby's participation in this study, you should notify Dr. Drover at 650-725-0364.

This research study is looking for 90 pregnant and the 90 babies born to these mothers, to complete this study. The study will be done at multiple sites (approximately 5-10 sites) across the United States of America with Stanford as the coordinating center. LPCH/Stanford Hospital expects to enroll up to 30 of the 90 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

Your baby's participation will start on his/her date of birth and will continue for five days while being treated with the study medication.

PROCEDURES

If you choose to allow your baby to participate, you must sign this consent form. The Protocol Director and his research study staff will explain the study in detail to you. If your baby's father is available, we will also obtain his written signature on this parental permission form. The following procedures for your baby will occur only after your written parental permission on this consent is obtained:

Baby's Participation Starts on Day of Birth:

1. **Samples of Blood from the Umbilical Cord:** venous cord blood will be obtained after the birth of your baby when the obstetrician cuts and clamps the cord; most umbilical cords are not saved, they are disposed of in the biohazard waste at Stanford but your signature on this consent allows us to obtain blood from the cord to measure how much ondansetron and ondansetron metabolites are in the cord blood.

2. **Screening 12-lead electrocardiogram (ECG):** to ensure the baby's heart is functioning normally prior to the first dose of study medication.

3. **Follow-up ECGs:** there will be a 12-lead ECG done following **each dose** of study medication (up to 5 doses) to check on your baby's heart rate and rhythm. Your baby may have as many as 6 ECGs for the study.

4. **Blood draw prior to first dose:** may be done either by a heel stick or when a routine heel stick is ordered; if no clinical blood draw is ordered, we would like to obtain one blood sample (0.1 ml or approximately 1-3 drops) by heel stick before starting the first dose of study medication.

5. **Study medication:** your baby will receive the same study medication you received prior to delivery, either placebo or ondansetron. The study medication for your baby will be given every 24 hours, orally (liquid syrup), for up to 5 days starting with the first dose given approximately4-8 hours after birth.

- Placebo is made from inactive, liquid syrup that will look identical to the oral ondansetron syrup. The placebo group of babies will be compared to the ondansetron group of babies.

- Ondansetron is an FDA approved drug for use in adults, pregnant women and in children as young as one month old, to prevent or treat nausea. In this study ondansetron is considered the "investigational" drug because we will be using it for a new reason, to try to prevent NAS in your baby. Ondansetron is not approved by the FDA for use in neonates; the only approved dosing for infants

as young as one-month old through 5 months old, is for a single dose given through the vein (IV), to treat nausea. We plan to give one dose per day for a total of 5 doses; most babies will start with oral study drug but it can also be given through the vein if that is the best way for your baby at the time. We hope to show that ondansetron can prevent NAS better than the placebo study medication.

6. **Blood samples after study medication is started:** the majority of samples for our research study will be obtained whenever a standard-of-care (routine) heel stick is ordered by your baby's medical doctors for standard clinical lab tests. We will limit our research blood samples to 9 in total. If no blood tests are ordered in the first 12 hours of your baby's life, we would like to obtain a sample of blood by heel stick at these time points: 1) prior to the first dose of study medication and 2) a second blood sample after the first dose of study medication but before your baby has become 12 hours old. Our research samples only require a few drops of blood (approximately 0.1 mL or 1-3 drops of blood) to be placed on our special filter paper

7. **Close observation for safety:** your baby will be closely observed for the possible development of symptoms of NAS according to the standard-of-care at Lucile Packard Children's Hospital.

8. **Treatment of NAS**: if your baby shows symptoms of NAS, he/she will be treated the same way he/she would be cared for whether or not he/she was on the study. Morphine is the current standard treatment for NAS symptoms, and is used by all the hospitals in this study. If necessary, other sedative-type drugs to help reduce their NAS symptoms will be given as standard of care by all the hospitals in this study.

   Any blood samples left over after analysis will be destroyed when the study is completed.

PARTICIPANT RESPONSIBILITIES

As a participant and spokesperson for your baby, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Be available for our daily phone calls after you are sent home.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you or the baby may have after you go home.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about allowing your baby to stay in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your baby's participation at any time. Your decision will not affect your ability to receive medical care for your baby's disease and you will not lose any benefits to which your baby would otherwise be entitled.

There is no risk to your baby if you change your mind and decide to stop the study early.

If you decide to withdraw your consent for your baby to participate in this study, or the study medication is stopped for any reason, there are no anticipated problems, but you should notify Dr. David Drover at 650-725-0364 as soon as possible.

The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your baby's participation could be harmful to your baby.
- Your baby needs treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

If your baby receives ondansetron as their study medication, the dose of ondansetron will be 0.07 mg/kg orally every 24 hours for up to 5 days (up to 5 doses maximum). If we need to give the study medication intravenously (IV), the dose will be 0.04 mg/kg every 24 hours IV. There is no FDA approved dosing of ondansetron for neonates at this time; the youngest infants to receive ondansetron in a controlled study were one month old. The FDA approved dose for infants as young as one month old, suffering from nausea, is 0.1 mg/kg IV, one time. We have chosen a lower dose, 0.04 mg/kg IV (less than one half of the FDA approved dose). However, we will be dosing the drug once per day for up to 5 days, to newborns, a new age group to receive this medication. We are not giving the newborn babies this study medication for nausea, we are using it to try and prevent NAS. Since the drug is given based on weight, the

less a baby weighs, the less study medication the baby will receive each day. The side effects of ondansetron are:

Common Reactions
* headache
* constipation
* fatigue
* diarrhea
* hypoxia (decrease in oxygen in your system)
* pyrexia (increased body temperature)
* urinary retention
* dizziness
* agitation
* pruritus (itching)

Serious Reactions
* severe hypersensitivity reaction
* anaphylaxis (extreme allergic reaction that can be life threatening)
* bronchospasm (spasm of the muscles around your "wind pipe")
* extrapyramidal symptoms (changes effecting the nerves controlling your motor activity)
* oculogyric crisis (uncontrolled rolling of your eyes)
* blindness, transient
* QTc prolongation (change in the way your heart beats)

The possible risks of obtaining blood samples from your baby are pain and bruising. Infection can also occur anytime the skin is broken to obtain samples, but this risk is extremely small as sterile supplies are used, and all hospital protocols are followed.

The 12-lead ECGs for your newborn baby poses no risk to the baby other than a very slight risk of possible skin irritation where the sticky pads are placed on the baby's skin.

This particular treatment may involve risks to the subject, which are currently unforeseeable.

POTENTIAL BENEFITS

If ondansetron successfully prevents or lessens the symptoms of NAS, your baby may benefit by having his/her symptoms eliminated or reduced.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

- The alternative is not to allow your baby to participate.
- We will not withhold any standard treatments for your baby.
- Please discuss the potential risks and benefits of not participating with a physician.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to allow your baby to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to allow your baby to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your baby's condition or your willingness to continue his/her participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

Your baby's identity & yours will be kept as confidential as possible as required by law. Your baby's personal health information related to this study may be disclosed as authorized by you. Your responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in this confidentiality statement of the consent, we do not intend to disclose this information. Your baby's research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your baby's identity will not be disclosed**.** We will do everything we can to keep others from learning about your baby's participation in this study. To further help us protect your baby's privacy, we received a Certificate of Confidentiality from the United States Department of Health and Human Services (DHHS) on Aug 21, 2013, which was prior to enrolling any participants.

With this Certificate, we cannot be forced (for example by court order or subpoena) to disclose information that may identify your baby in any federal, state, local, civil, criminal, legislative, administrative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you or your child, except to prevent serious harm to your baby or others, and as explained below.

You should understand that a Certificate of Confidentiality does not prevent you, or a member of your family, from voluntarily releasing information about yourself, your child, or your involvement in this study.

If an insurer or employer learns about you or your baby's participation, and obtains your consent to receive research information, then we may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to determine if the drug ondansetron, if given to babies born to narcotic-dependent mothers, will prevent those babies from suffering from a syndrome called "Neonatal Abstinence Syndrome", also called "NAS". We hope to learn if we can prevent NAS by first giving these pregnant narcotic-dependent women a dose of intravenous (IV) ondansetron prior to the delivery of their babies, followed by giving the newborn babies a dose of ondansetron once a day for up to 5 days. Currently there is no standard-of-care medicine used to "prevent NAS" and babies are only treated once they suffer the symptoms of withdrawal from narcotics. Because this is a clinical trial, the information will be submitted to the sponsor, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA).

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, your baby will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your baby's health information (and to discontinue any other participation in the study) at any time. After any revocation, your baby's health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your baby's health information in this study, you must write to: David R. Drover, MD. Stanford Medical Center, Anesthesia Department, MC 5117, 300 Pasteur Drive, Stanford, CA 94305.

What Personal Information Will Be Obtained, Used or Disclosed?
Your baby's health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to: up to 9 blood samples for analysis of ondansetron, gestational age, mode of delivery, birth weight, birth length, medical record number, 12-lead ECGs, Apgar scores at 1 min and 5 min, gender, date of birth, amount of narcotic needed to treat NAS, length of stay in hospital, Modified Finnegan scores, need for medical treatment of NAS; need for barbiturate treatment of NAS; duration of medical treatment of NAS; weight change during hospitalization; frequency and duration of breast/bottle feeding in hospital and at home after discharge; and all other medications used to treat NAS.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your baby's health information in connection with this research study:

- The Protocol Director, David Drover, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health (NIH)
- The Food and Drug Administration (FDA)
- Data Safety Monitoring Board

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on (December 31, 2025) or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ ___ _____
Signature of Legally Authorized Representative Date
(e.g., parent, guardian or conservator)

_____
Description of Representative's Authority to Act for Neonatal Participant

Print Name of LAR: _____

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs

If your baby participates in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study.

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and care that you require during this study for routine medical care. **You will be responsible for any co-payments and/or deductibles as required by your insurance.**

Sponsor

The National Institutes of Health (NIH) is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. David Drover at (650) 725-0364.

You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, MC 5579, Palo Alto, CA 94306.

Alternate Contact: If you cannot reach the Protocol Director, please contact Dr. Brendan Carvalho at 650-861-8607 or pager number 650-723-8222, ID #13980.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ☐Yes ☐No

Signing your name below means you agree to allow your newborn baby to be in this study once he/she is born.

_____ _____
Signature of LAR (Parent, Guardian or Conservator of the Neonatal Participant) Date

_____ _____
Authority to act for the Neonatal Participant Printed Name of LAR

_____ _____
Signature of Other LAR (Parent, Guardian or Conservator of the Neonatal Participant) Date

_____ _____
Authority to act for Neonatal Participant Printed Name of Other LAR

The IRB determined that the permission of one parent is sufficient for research in accordance with 21 CFR 50.55.

_____ _____
Signature of Person Obtaining Consent Date

Print Name of Person Obtaining Consent: _____

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of witness Date

Print Name of Witness: _____

(e.g., staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.
- The English consent form (referred to as the "Summary Form" in the regulations):
  - Must be signed by the witness AND the Person Obtaining Consent (POC).
  - The non-English speaking participant/LAR does not sign the English consent.
  - The non-English speaking participant/LAR should not sign the HIPAA participant line
  - If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.