# Document Coversheet

Study Title: Non-Opiate Treatment After Prenatal Opiate Exposure to Prevent Postnatal Injury to the Young Brain (No-POPPY)

| | |
|---|---|
| Institution/Site: | University of Kentucky |
| Document (Approval/Update) Date: | 12/17/2024 |
| NCT Number: | NCT03396588 |
| IRB Number | 43976 |
| Coversheet created: | 3/27/2025 |

**IMPORTANT NOTE: If you select the wrong IRB type or "Protocol Process Type" while your *Initial Review (IR)* application is in draft, or if your IR application has been returned to you for requested revisions or additional information, you may change your selections. You will not be able to change your selections for "Which IRB" or "Protocol Process Type" after initial *approval* of your application (the option to change your selections is not available for MR or CR).**

For guidance, see:

- Which IRB?
- Which Protocol Process Type?
- "Getting Started"

**Please contact the Office of Research Integrity (ORI) at 859-257-9428, IRBsubmission@uky.edu, or request a consult to resolve any questions regarding your selections *prior* to submitting your Initial Review application.**

Which IRB

- (•) Medical ( ) NonMedical

Protocol Process Type

- ( ) Exemption
- (•) Expedited (Must be risk level 1)
- ( ) Full

**The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.**

**EXPEDITED CERTIFICATION**

**0 unresolved comment(s)**

**To Be Completed Only If Protocol is to Receive Expedited Review**

**Applicability**

A. Research activities that (1) present no more than *minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

**"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. 45 CFR 46.102(i)*

Check the appropriate categories that apply to your research project:

☑ Study was originally approved by the full IRB at a convened meeting.

☐ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

A. Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
B. Research on medical devices for which (i) an investigational device exemption application is not required*; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.**

* Study must meet one of the IDE Exempt categories listed on the Device Form Attachment.
** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements.
NOTE: Select Category 1 for compassionate use medical device applications or individual patient expanded access investigational drug applications for which FDA has waived the requirement for full review.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

A. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
B. From other adults and children* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves "minimal risk".

*In Kentucky, "child/children" refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Informed Consent SOP for discussion of "Emancipated Individuals" under Kentucky state law.) Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., DHHS, FDA, and U.S. Department of Education). Children are defined in the HHS regulations as "persons who have 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." If conducting research outside the state of Kentucky, you are responsible for complying with applicable state law.

☐ 3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

A. Hair and nail clippings in a nondisfiguring manner;
B. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
C. Permanent teeth if routine patient care indicates a need for extraction;
D. Excreta and external secretions (including sweat);
E. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
F. placenta removed at delivery;
G. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
H. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
I. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
J. Sputum collected after saline mist nebulization.

☐ 4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

A. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
B. Weighing or testing sensory acuity;
C. Magnetic resonance imaging;
D. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
E. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☐ 5) Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for non-research purposes (such as medical treatment or diagnosis) as well as research involving existing information or specimens that were previously collected for research purposes, provided they were not collected for the currently proposed research. (Note: Some research in this category may qualify for Exempt review. This listing refers only to research that is not exempt.)
(Note: If submission includes materials previously collected for either non-research or research purposes in a protocol for which IRB approval expired, you may check Category 5. However, a separate category must also be selected for prospective collection of data/specimens obtained solely for research purposes)

☐ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)

**MODIFICATION REQUEST SECTION**

**0 unresolved comment(s)**

***** If this modification changes the scope of your activities to include COVID-19 related research, please insert "COVID19" at the start of your Project and Short Titles.*****

Select One:

- (•) This modification does not increase risk to study participants.
- ( ) This modification may or will increase risk to study participants.

Is this modification request due to an Unanticipated Problem/Adverse Event, or Protocol Violation?

- ( ) Yes (•) No

In your professional opinion, does this modification involve information that might relate to a subject's willingness to continue to take part in the research?

- ( ) Yes (•) No

If yes, state how the information will be communicated to subjects (i.e., re-consent, send letter, etc.):

**For each proposed modification, include a justification.**

Example: Jane Doe, MD, is being added as co-investigator because she has expertise with the subjects on this protocol. She has completed human subject protections training, and is authorized to obtain consent.

Anthony Mangino PhD is being added to assist with data analysis. He has completed HSP and RCR trainings.

**PROJECT INFORMATION**

**0 unresolved comment(s)**

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Non-Opiate treatment after Prenatal Opiate Exposure to Prevent Postnatal Injury to the Young Brain (No-POPPY)

**Short Title Description**
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

Non-Opiate treatment after Prenatal Opiate Exposur

Anticipated Ending Date of Research Project: 12/31/2025

Maximum number of human subjects (or records/specimens to be reviewed) 1000

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

Are you requesting that the UK IRB serve as the lead IRB for a multi-site study, **OR** that the UK IRB defer review to another IRB? [Click here for "IRB Reliance" help]
○ Yes ◉ No
**If "Yes," before completing your IRB application, fill out the Reliance Request Form and submit it to irbreliance@uky.edu.**

## PI CONTACT INFORMATION

**0 unresolved comment(s)**

**Principal Investigator (PI) role for E-IRB access**
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be listed as PI here.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

The Principal Investigator's (PI) contact information is filled in automatically based on who logged in to create the application.

**If you are not the Principal Investigator, do NOT add yourself as study personnel.**
To change the PI contact information on an application in Researcher edit status:

- click "Change Principal Investigator";
- search for the PI's name using the search feature;
- click "Select" by the name of the Principal Investigator, then "Save Contact Information".

You will automatically be added as study personnel with editing permissions to continue editing the application.

**Change Principal Investigator:**

| | | | |
|---|---|---|---|
| First Name: | Henrietta | Room# & Bldg: | Basement Room 007, Leader Ave. Building |
| Last Name: | Bada | Speed Sort#: | 405360298 |
| Middle Name | S | | |
| Department: | Pediatrics - 7H650 | Dept Code: | 7H650 |
| PI's Employee/Student ID#: | 00032491 | Rank: | |
| PI's Telephone #: | 859-323-1019 | Degree: | MD |
| PI's e-mail address: | hbada2@email.uky.edu | PI's FAX Number: | |
| PI is R.N. | ○ Yes ◉ No | HSP Trained: | Yes |
| | | HSP Trained Date: | 5/23/2024 |
| | | RCR Trained: | Yes |

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

**RISK LEVEL**

**0 unresolved comment(s)**

Indicate which of the categories listed below accurately describes this protocol

- (●) (Risk Level 1) Not greater than minimal risk
- ( ) (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ( ) (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ( ) (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

***For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).***

Refer to UK's guidance document on assessing the research risk for additional information.

**SUBJECT DEMOGRAPHICS** **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc.) newborn to 100 years

**Study Population:**

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

Cohort 1 will include infants exposed to opiates while in utero and requiring pharmacologic treatment to treat their withdrawal symptoms. Treatment of these NAS symptoms will use a randomized and double-blind study design to compare the use of opiate (morphine) and/or non-opiate (clonidine). Cohort 2 will include infants exposed to opiates in utero but not requiring pharmacologic treatment based on Finnegan scores. Cohort 3 and 4 will include infants not exposed to opiates by maternal history or negative drug screen and serve as a control group.
The study is expected to start screening and enrolling infants beginning around December 2017.The study is expected to end in March 2022 after all follow-up care has been completed. The parents of subjects who meet criteria will be approached for consent. The Kentucky Children's Hospital has an 88% Caucasian, 5% African American, 4% Hispanic, and 3% other race/ethnicity breakdown.
Due to the nature of the information collected from the caretakers via interview questionnaires and chart review, each mother and/or caretaker will be considered an additional study subject. This brings the estimated total of research subjects to approximately 1,000 participants. Please see the attachment "breakdown chart of study population."

The University of Tennessee Health Science Center has a population of about 80% African American, 16% Caucasian, and 0.5% Hispanic individuals. UTHSC will contribute approximately 40 of the 1,000 participants.

CBCL cohort: The cohort of subjects approached for the CBCL follow up will only be subjects in cohort 1 at the University of Kentucky.
We will not be enrolling any additional infants, but will be reaching out to families (parents, guardians, etc.) who meet the following qualifications:
- have signed consent and agreed to be contacted by the research team for future research
- do not have any follow up data from research interviews/NICU grad clinic OR did not have any follow up data within the 24M window
- are <5 years of age
Families will be excluded if they meet any of the following:
- signed consent and did not agree to be contacted for future research
- have completed follow up visits
- are >5 years of age
- are currently in custody of guardian(s) other than those who signed consent for the study originally
- are incarcerated

Patients will be initially contacted by phone using the number(s) given at time of consent. If family is interested in participating, they will be sent a survey invitation to their email address.

Attachments

| Attach Type | File Name |
|---|---|
| StudyPopulation | breakdown chart of study population.pdf |

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
**(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):**

**Participant Demographics**

| | Cisgender Man | Cisgender Woman | TGNB/TGE | Unknown/Not Reported |
|---|---|---|---|---|
| American Indian/Alaskan Native: | 0 | 0 | | |
| Asian: | 1 | 1 | | |
| Black/African American: | 15 | 45 | | |
| Latinx: | 8 | 22 | | |
| Native Hawaiian/Pacific Islander: | 0 | 0 | | |
| White: | 222 | 662 | | |
| American | | | | |

| | | | | |
|---|---|---|---|---|
| Arab/Middle Eastern/North African: | 1 | | | |
| Indigenous People Around the World: | | | | |
| More than One Race: | | | | |
| Unknown or Not Reported: | 8 | 23 | | |

If unknown, please explain why:

"Unknown" refers to those of more than one race. Planned enrollment includes both treated and non-treated infants, mothers and foster parents interviewed, and control infants.

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☑ Children (individuals under age 18)
- ☑ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☑ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☑ Appalachian Population

***ADDITIONAL INFORMATION:***

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

**Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):**

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

**Examples of such conditions include:**

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

**SUBJECT CHILDREN**

**0 unresolved comment(s)**

**SECTION 1. Risk Level**

Complete this section and include it with your IRB application submission. *In Kentucky, a child is an individual less than 18 years of age unless the individual is legally emancipated.*

Note: the explanation(s) you are being asked to provide in Section 1 correlate(s) to the risk level you selected in the Risk Level section.

**Minimal risk means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life *of a healthy child* or during the performance of routine physical or psychological exams or tests.**

**FOR FDA REGULATED RESEARCH:** Based on the 2013 FDA final rule Subpart D, a placebo control arm of a clinical trial must be approved under either Risk Category 1, Risk Category 3], or Risk Category 4 ]. FDA does not consider administration of a placebo to offer a prospect of direct benefit to an individual subject under Subpart D, Risk Category 2 [21 CFR 50.52].

**Not involve greater than minimal risk.**

**In the Risk Level section of the IRB Application you indicated your research does not involve greater than minimal risk.**

A. Explain why your research does not involve greater than minimal risk:

This study is closed to enrollment and involves only data analysis.

**SECTION 2. Assessment and Evaluation of the Risks**

For details, refer to the UK IRB's Policy on Children in Research.

A. Provide justification for the participation of children as research subjects in your study.

Neonatal Abstinence Syndrome (NAS) is a disease of newborns - the study population for this trial.

B. Has this research been conducted in adults? ○ Yes ◉ No

If yes, is there any indication that the proposed research would benefit, or at least not be harmful to children?

C. Indicate how many children you propose to enroll in the study: 330

**Note:** Whenever possible, involve the fewest number of children necessary to obtain statistically significant data which will contribute to a meaningful analysis relative to the purpose of the study.

Justify this number:

An earlier pilot trial enrolled 30 babies which gave preliminary data to look at the current larger trial. 250 enrolled (treated) patients will provide an appropriate power analysis. We propose to enroll 50 consented/untreated babies and 30 control/well-babies to provide appropriate power analyses for those two cohorts.

D. Check all that apply:

- ☐ My research involves children 6 years of age or older.
- ☑ My research involves children under 6 years of age.

Indicate how assent will be solicited by selecting all that apply:

Assent will be solicited from: ○ All Children ○ Sub-group of children ○ None of the children

I am requesting waiver of the requirement for assent from: ○ All Children ○ Sub-group of children ○ N/A

Indicate justification for waiving assent for these children: (Check all that apply)

- ☐ 1. The intervention or prospect involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child/children and is available only in the context of the research.
- ☐ 2. The children are not capable of providing assent based on the age, maturity, or psychological state.
- ☐ 3. The capability of the children is so limited that they cannot reasonably be consulted
- ☐ 4. Other (explain)

** If you checked question 3, please explain:

** If you checked question 4, please explain:

E. Unless you are requesting a waiver of the requirement for assent for ALL children, you must answer "yes" to at least one of the following two statements.

**Note:** All assent forms or scripts must be attached to the "Informed Consent" section of this application. Be sure to save your responses in this section first.

For Children 6-11:
Assent will be obtained verbally. I have attached an assent script for obtaining verbal assent for IRB review.

○ Yes ◉ No

For Children 12-17:
The children will document assent by signing an assent form, or provide assent verbally if approved by the IRB, depending on the circumstances outlined in the application. I have attached an assent form or script for IRB review.

○ Yes ◉ No

F. Explain how study personnel will evaluate dissent (e.g., behaviors that would indicate the child does not want to participate such as moving away, certain facial expressions, head movements, etc.). If your study involves only children under 6 years of age, enter "N/A" below.

N/A

G. Describe how parental permission will be obtained.

Biological parent(s) will be approached for consent by either a member of the medical care team or a research nurse, who will summarize the research to the parent(s). First, the study will be described and explained to them. The content of the informed consent will be read to the parent(s) if necessary. The parent(s) will receive a copy of the consent, and will be encouraged to review the consent in private. If the parent(s) express willingness to enroll their child in the study, the parent will be asked to sign the informed consent. Only mothers greater than age 18 will be approached for this study, assent will not apply.

If parental rights are terminated after the initial consent is signed, the legal guardian(s) will be approached for re-consent.

"Outborn" informed consent may be obtained by any of the following methods:
• The UK Neonatal Transport Team will be able give the parent(s) a copy of the informed consent when they arrive at the outside institution. The UK physician or research team will then call to discuss the consent with the family member. The Transport Team will bring a signed consent form back to UK, or it will be faxed to UK if consent is obtained.
• The attending physician and or research team may also contact the parent(s) by phone at the delivery hospital, fax the consent/HIPAA to the nurse's station, discuss the consent by phone, either fax the consent back to UK or give to the Transport Team.
If the infant does not require immediate treatment, it may be possible to obtain consent when the parents visit after the baby is admitted to UK.

I have attached a parental permission form for IRB review. ◉ Yes ○ No

Parental permission forms must be attached in the "Informed Consent" section of this application. Be sure to save your responses in this section first.

**Note that for Risk Category 3 or Risk Category 4 where research involves more than minimal risk without the prospect of direct benefit to the individual child, the permissions of both parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available OR or only one parent has legal responsibility for the care and custody of the child.)**

I am requesting

☐ The permission of 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. **(required for Risk Category 3 or Category 4 Research).**

☑ The permission of one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. **(permitted for Risk Category 1 or Category 2 Research).**

☐ Waiver of the requirement for signatures on parental permission forms. (Complete the "Request for Waiver of Signatures" questions in the in the Informed Consent/Assent Process/Waivers Section)

☐ Waiver of the requirement for parental permission.

**Note:** Parental/guardian permission cannot be waived for FDA regulated studies that are greater than minimal risk (Risk Categories 2-4).

Parental Permission Waiver Options

○ Complete the "Request for Waiver of Informed Consent Process" questions in the Informed Consent/Assent Process/Waivers Section.

○ Justify that the research study is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable request (e.g., abused children):

Justify:

H. Describe how study personnel will ensure that a parent is present when the child participates in any research activities.
*Note: If the nature of the research is such that it is not appropriate to have a parent present (e.g., research into sensitive personal issues, physical examinations of teenagers, etc.), explain why.*

Enrolled patients are in the NICU and/or NACU. Parents are encouraged to remain with the patient and be involved in their daily care and decision making, however, this treatment may take up to 3 months to resolve the symptoms of NAS. For follow-up developmental assessments (taking place at 6-8 months, 12-14 months, and 24-26 months), parent(s) or legal guardian(s) will be present.

I. Describe the study personnel expertise for dealing with children at the ages included and whether they are knowledgeable and sensitive to the physical and psychological needs of the children and their families. Explain how the facility in which the research will be conducted is appropriate in relation to environment and/or equipment accommodating to children.

Assessments are completed by research nurses who have past NICU bedside experience and have received specialized training and certification in study assessments. Follow-up assessments occur at the UK NICU Graduate clinic, which is a specialty clinic staffed by professionals who specialize in follow-up and developmental outcomes. The Kentucky Children's Hospital NICU admits up to 1,000 infants each year, and in 2016 there were 170 infants diagnosed with NAS. There is now a designated NAS unit (NACU- Neonatal Abstinence Care Unit) that specializes in the care of NAS patients.

J. If applicable, provide additional information that may support your request to involve children in research.

Neonatal Abstinence Syndrome is a growing problem in the United States, and the treatment methods vary according to the particular drug of use in mothers. Finding a better treatment option would potentially create a shorter length of stay and improve developmental outcomes.

**SECTION 3. Wards of the State**

If you need to activate this section:

- go to the Subject Demographics section;
- select "Wards of State (Children)" in the categories of subjects and controls to be included in your study;
- save that section.

**A. 45 CFR 46.409(a)**

Please indicate which category describes your research proposal:

- ○ Research is related to subjects' status as ward of the state.
- ◉ Research is conducted in schools, hospitals, or similar setting(s) in which the majority of children involved in the study are NOT wards.

**B. 45 CFR 46.409(b)**

Federal regulations state that an advocate must be appointed in circumstances where investigators enroll wards of the state for research studies which are greater than minimal risk **specifically risk category 3 or 4.** Please answer the following questions:

a) Will the advocate serve in addition to a guardian or in loco parents?

◉ Yes ○ No

b) Check the applicable item:

- ◉ Each child will have their own advocate.
- ○ One advocate will serve for all children enrolled in the study.
- ○ N/A

c) Explain why the advocate has the background and experience to serve as an advocate for the study.

Each child is appointed a state social worker per DCBS protocols.

d) Federal regulations state that an advocate cannot be associated with the study, investigator or organization. Please provide assurances that the advocate does not meet any of the criteria listed above.

The state social workers are appointed by DCBS and have no affiliation to the University.

**SECTION 4. Children Located Outside the State of Kentucky**

Does your study involve children outside the state of Kentucky? ◉ Yes ○ No

Provide information regarding the state definition of legally authorized representative, child, or guardian, as applicable to the research and to the federal definitions. [If the research is to be conducted in more than one state outside of Kentucky, provide this information for each state.]:

Per UTHSC SOP (added as attachment) definition:
"Legal Guardian means an individual who is authorized by a court under applicable state or local law to consent on behalf of a child to general medical care. The term "legal guardian" as used here does not include non-custodial parents, grandparents, adult siblings, step-parents or other adult family members, unless such individuals are authorized by a court of law to make decisions about general medical care for the child."

**Guidance on Consent and/or Authorization by a Legally Authorized Representative**

Consistent with Kentucky health care decision statutes for choosing a legally authorized representative for children, the following responsible parties in the order of priority listed shall be authorized to make research participation decisions on behalf of the child: (a) the judicially-appointed guardian of the person, if the guardian has been appointed and if the decisions to be made under the consent are within the scope of the guardianship; (b) the parent of the child.

**Definitions**

For definitions of "child/children", emancipated individuals, "legally authorized representative", "guardian", "assent", and "permission", see the ORI/IRB Informed Consent Standard Operating Procedures (SOP).

**PRISONERS**

**0 unresolved comment(s)**

**SECTION 1.**

For studies involving **prisoners** or people at risk of becoming involuntarily detained during the research (e.g., subjects with substance abuse history), respond to the following items. For information on restrictions and regulatory requirements, see ORI's Research Involving Prisoners web page.

For research involving prisoners, the definition of minimal risk refers to 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.

Select the category below that best represents your research and explain why your research meets the criteria.

Prisoner Categories

- (●) **Category 1: My research involves the study of possible causes, effects, processes of incarceration, and of criminal behavior.** (Processes of incarceration can be interpreted broadly to include substance abuse research, half-way houses, counseling techniques, criminal behavior, etc.)
- ( ) **Category 2: My research involves the study of prisons as institutional structures, or of prisoners as incarcerated persons.** (This category is usually used fairly narrowly – i.e., looking at prisoner diet, conditions of prison, etc.)
- ( ) **Category 3: My research involves the study of conditions particularly affecting prisoners as a class.** (This category is rarely used – e.g., vaccine trials, research on hepatitis, social and psychological problems such as alcoholism, drug addiction, sexual assaults. Minimal risk studies should not go under this category.)
- ( ) **Category 4: My research involves the study of practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.** (Rare for research involving placebo or control groups to fall in this category because of the difficulty in justifying improvement of the health or well-being of the subject being given placebo or in a control group.) Note: Contact the Office of Research Integrity at (859) 257-9428 for more information.
- ( ) **Epidemiologic Research Involving Prisoners [See also SECTION 3 below]**

Justify how the research presents no more than minimal risk and no more than inconvenience to the subjects:

The research activities involved with this project are maternal interviews that include questions about sensitive information regarding the mothers of our research participants that might illicit emotional response. There is a certificate of confidentiality approved for this information that prohibits the research personnel from disclosing this information to anyone, including law enforcement, healthcare providers and social services.

**SECTION 2.**

When an IRB is reviewing a protocol in which a prisoner will be a subject, the IRB must find and document justification that six additional conditions are met. Describe in the space provided how each condition applies to your research.

NOTE: If your study **only** involves epidemiologic research, you may insert "N/A" in each of the text boxes in this section (Section 2). Your response to Section 3 will determine appropriateness for "N/A" answers here.

**Condition 1.** Advantages acquired through participation in the research, when compared to the prisoners' current situation, are not so great that they impair their ability to weigh risks.
***Describe the possible advantages that can be expected for prisoner participants:***

Some potentially eligible study subjects (babies born exposed to opiates) may have an incarcerated mother. Their mothers' status as a prisoner should not limit the newborns' opportunity to participate in the study.
Prisoners' babies, who have been exposed to opiates in-utero, have the option to partake in a study comparing opiate versus non-opiate treatment. The prisoners have the option of choosing to enroll their babies in the study, which offers the opportunity to receive an alternate to standard opiate treatment. Non-opiate treatment may not pose the potential effects of continued opiate use on the developing brain.

**Condition 2.** Risks are the same as those that would be accepted by non-prisoners.
***Describe the possible risks that can be expected for prisoner participants and justify that they are the same as for non-prisoners:***

Prisoners will only be asked to complete a "maternal interview," which is an observational survey regarding social behaviors that include substance use history. The study has received a Certificate of Confidentiality so no disclosure of illegal activities, including substance use or illegal activities, will be reported.
All mothers of babies enrolled in the study are asked to complete the same set of surveys. Prisoners and non-prisoners receive the same questionnaires. Psychological and social risks may come up during interviews with substance abusing mothers, regardless of prisoner status, but this risk would be the same if they were not part of the study.

**Condition 3.** Procedures for selection are fair to all prisoners and are immune from intervention by prison authorities in prisons; control subjects must be randomly selected.

***a) Describe how prisoners will be selected for participation:***

The KCH saw 170 newborns admitted with NAS in 2016, and many are diagnosed at delivery with the potential for withdrawal symptoms as a result to in-utero opiate exposure. Babies born at referral hospitals are sent to the UK NICU during the first week due to severity of symptoms. Co-investigators that include attending physicians and fellows caring for these babies are aware of the study enrollment criteria and alert research staff should an eligible participant present. Further, study research nurses complete a "pre-screen" of potentially eligible subjects by examining electronic medical records of admitted babies and mothers. Prisoners' babies are selected for participation not due to their status as prisoners, but as a result of their babies being born exposed to opiates. Mothers who are prisoners will have equal opportunity as non-incarcerated mothers to have their babies participate in the study. Their status as prisoners will not affect their ability to participate or for their babies to receive treatment if needed.

***b) Describe what measures will be taken to prevent intervention by prison authorities in the selection process:***

The co-investigators, who are the attending physicians and fellows, and the research nurses identify potentially eligible participants through a chart review of admitted newborns. There is no interaction with any prison authority throughout this process. Prison authorities have no say in the mothers' decision to enroll their babies in the study or for their opportunity to complete maternal surveys.

**Condition 4.** Parole boards cannot take into consideration a prisoner's participation in research. Informed consent must state participation will not impact parole.
***Describe what measures are in place to ensure parole boards are not influenced by prisoners' participation in research and how prisoners will be told their participation (or refusal or withdrawal from) will not impact parole:***

The prisoners contribute to this research project in the form of completing social/behavioral questionnaires that take between 30-45 minutes to complete. This interview typically occurs while the mother is admitted following delivery. Prisoners are not the subjects studied, but are considered part of the mother/infant dyad. Mothers/prisoners provide information that will later provide researchers with a better understanding of the social/behavioral factors influencing babies in the study. Researchers will not be in contact with parole boards or prisoner/legal authorities at any point.

**Condition 5.** For studies that require follow-up, provisions are made including consideration for the length of individual sentences; informed consent must reflect provisions for follow-up.
***Describe what provisions have been made for follow-up and how this information will be relayed to the prisoner participants:***

Follow-up of babies enrolled in the study will be conducted with the guardian and/or whomever brings the baby to their follow-up appointment. This may or may not be the mother interviewed initially. The interviews conducted at follow-up will take place with the guardian. Follow-up with the prisoner will only take place if the prisoner attends clinic follow-up appointments with the baby, meaning that she is no longer incarcerated.

**Condition 6.** Information about the study is presented in a language understandable to prisoners.
***Describe what efforts have been made to present information about the study in a language understandable to the prisoner population:***

The consent form and verbal descriptions used to explain the study to prisoners include language and descriptions that keep low health literacy and low literacy in mind. Prisoners are provided with the opportunity to ask as many questions as they have, and research staff will take their time in explaining the study and providing alternative descriptions (i.e., a different way of explaining themselves if the initial explanation is indicated to be unclear). Study staff will ask the mothers/prisoners to repeat back their understanding of the study. No participant will be enrolled if there is any indication that the mother does not understand the study.

**SECTION 3. Epidemiologic Research Involving Prisoners**
**Only complete if applicable:**

Effective June 20, 2003, DHHS adopted policy that allows waiver of the requirement for documenting applicability of a category (as found in Section 1 of this form) for certain epidemiologic research involving prisoners. This waiver applies to epidemiologic research on prisoners that presents no more than minimal risk and no more than inconvenience to the prisoner-subjects.

☐ Check this box if your research meets all three criteria listed below, then provide justification in the space provided.

1. I request a waiver for meeting the category conditions under Section 1 of this form.
2. My research involves epidemiologic research intended to describe the prevalence/incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease; **and**
3. Prisoners are not the sole focus of my research.

Justify how the research presents no more than minimal risk and no more than inconvenience to the subjects:

**SECTION 4. Prisoners are not the targeted population**
**Only complete if applicable:**

Although prisoners may not be the target population for your research, a subject could become a prisoner during the course of the study (particularly if studying a subject population at high-risk of incarceration).

**Note:** If you did not receive IRB approval for involvement of prisoners, and a subject becomes a prisoner during the study, **all research activities involving the now-incarcerated participant must cease** until IRB approval has been issued for their continuation in the research. If you need IRB approval for a prisoner subject to continue participation in your research, select and

complete the applicable category from Section 1, complete section 2 and this section, then submit for IRB review.

*In special circumstances where it is in the best interest of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research prior to satisfying the requirements of Subpart C. However, subsequent IRB review and approval of this completed form is required.*

☐ Prisoners are not a target population for my research, but a subject became a prisoner during the study and I am seeking IRB approval so the subject can continue participation in the research.

Explain the importance of continuing to intervene, interact, or collect identifiable private information during the participant's incarceration:

**SECTION 5. Kentucky (KY) Department of Corrections (DoC) Approval**

Review the following conditions and determine whether any apply to your study:

- active recruitment of participants from a correctional facility (prison, jail, or community corrections institution);
- active recruitment of individuals under community supervision from a state probation and parole office.

If any of the above conditions apply to your research, refer to the Kentucky Department of Corrections Policy and Procedures, Management Information and Research (Chapter 5) for information about submitting a proposal for DoC approval of research including the DoC approved Research Consent and Research Agreement (5.1.G.1).

If the Department of Corrections is directly involved in your research as a sponsor or otherwise, contact Office of Legal Counsel at 859-257-2936 or email at UKOfficeofLegalCounsel@uky.edu and ask to be connected with a research attorney for additional information.

## INFORMED CONSENT/ASSENT PROCESS/WAIVER

**0 unresolved comment(s)**

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

**Consent/Assent Tips:**

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

**How to Get the Section Check Mark**

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF.**
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☑ Stamped Consent Doc(s) Not Needed

Attachments

**Informed Consent Process:**

Using active voice, in the text box below, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Will electronic consent form/process be utilized on-site or remotely for this study?

○ Yes ◉ No

If yes, in addition to addressing the above bullet points, describe the e-consent method and platform, including any hyperlinks, videos, or enhancements used to convey information, if applicable. Attach a representation of the e-consent with signature fields. For guidance, see the ORI E-Consent web page.

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

The subject's parent(s) will be approached for consent by either a member of the medical care team or a research nurse. The research nurse and/or a member of the medical team will summarize the research to the parent(s), and with family members if desired. First, the study will be described and explained to them. The content of the informed consent will be read to the parent(s) if necessary. The parent(s) will receive a copy of the consent, and will be encouraged to review the consent in private. If the parent(s) express willingness to enroll their child in the study, the parent will be asked to sign the informed consent. Mothers must be 18 years of age or older to consent for this study. Infants whose parent(s) do not speak English will not be included in this trial.
About 40-50% of the NAS admissions to the Kentucky Children's Hospital are referred from other nurseries in Central and Eastern Kentucky. "Outborn" informed consent may be obtained by any of the following methods:
• The UK Neonatal Transport Team will be able give the parent(s) a copy of the informed consent when they arrive at the outside institution. The UK physician or research team will then call to discuss the consent with the family member. The Transport Team will bring a signed consent form back to UK, or it will be faxed to UK.
• The attending physician and or research team may also contact the parent(s) by phone at the delivery hospital, fax the consent/HIPAA to the nurse's station, discuss the consent by phone, either fax the consent back to UK or give to the Transport Team.
• If the infant does not require immediate treatment, it may be possible to obtain consent when the parents visit after the baby is admitted to UK.

If/when a child is identified as a "ward of the state" and placed in custody of a foster parent, that new caretaker will then be approached and consented for the research study, this is in addition to the biological parents consent. The infant is appointed an individual social worker to provide as an advocate for the child's best interest. The new caretaker and social worker then have the option to choose to continue with the study procedures or withdraw from the study.

Occasionally, incarcerated mothers who may be eligible for the study may give birth at University of Kentucky Healthcare Kentucky Children's Healthcare. These mothers will be presented with the opportunity to participate in the study and for their babies to receive study drug. In the case where incarcerated mothers are not the caretaker who brings baby to follow up visits, the caretaker will re-consent and provide caretaker interview. This person will also receive follow up reimbursement. If an enrollee is a prisoner, their decision to participate or not to participate will in no way benefit or hurt their status with the prison system, the Department of Corrections, or the parole board.Of note, no incarcerated mothers will be enrolled at UTHSC.

At UTHSC, if/when a child is identified as a "ward of the state" and placed in custody of a foster parent, that new caretaker will then be approached and consented for the research study, this is in addition to the biological parents consent. The infant is appointed an individual social worker to provide as an advocate for the child's best interest. The new caretaker and social worker then have the option to choose to continue with the study procedures or withdraw from the study.

Addendum: Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose.
The principal investigator, Dr. Bada, will be responsible for handling complaints or request for information about research. Should

complaints or requests for information occur, the principal investigator will meet with the parent(s) and or designated representatives to go over the research procedures, risks, benefits, etc. and to answer questions related to the research. These meetings will be carried out assuring the parent(s) and or designated representative confidentiality of information. Subjects who do not wish to talk to the study staff/PI regarding their questions/concerns or with additional questions/concerns after talking with the PI will be given the number listed in the consent form for the ORI and will be encouraged to contact that number.

The sub-recipient principal investigator, Massroor Pourcyrous, M.D., will be responsible for handling complaints or request for information about research for all subjects at UTHSC.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

**SECTION 1.**

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

**SECTION 2.**

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

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

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

☑ Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

○ **Option 1**

**Describe how your study meets these criteria:**

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

◉ **Option 2**

**Describe how your study meets these criteria:**

a) The research presents no more than minimal risk to the participant:

Only for the CBCL follow up: These patients have already consented to the study and will be approached only for completion of this questionnaire. No identifiable information will be collected, and patients already have a study ID that will be used to connect the questionnaire response to the subject.

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

The CBCL is routinely used in the NICU grad clinic at UK as part of developmental assessments. Written consent is not sought for completing this standard of care. The purpose of the CBCL will be included in the cover letter provided to guardians.

○ **Option 3**

**Describe how your study meets these criteria:**

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

**STUDY PERSONNEL** **0 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
**After selecting 'Yes' or 'No' you must click the 'Save Study Personnel Information' button.**

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

**NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Getting Started page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (HSPTrainingSupport@uky.edu) for credit.**

**Study personnel assisting in research project:**

| Last Name | First Name | Responsibility In Project | Role | AC | Contact | Degree | StatusFlag | (HSP) | (HSP)Date | (RCR) | Removed? | Last Updated | SFI | Active |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ballard | Hubert | Co-Investigator | SP | Y | N | MD | P | Y | 12/14/2023 | Y | N | 02/22/2018 | N | Y |
| Bauer | John | Co-Investigator | SP | N | N | PhD | P | Y | 07/30/2023 | Y | N | 02/22/2018 | N | Y |
| Bhandary | Prasad | Co-Investigator | SP | Y | N | MD | P | Y | 03/03/2023 | Y | N | 02/22/2018 | N | Y |
| Camp | Gail | Study Coordinator | SP | Y | N | RN, CCRC | N | Y | 03/03/3000 | | N | 03/10/2021 | N | Y |
| Charnigo | Richard | Co-Investigator | SP | N | N | PhD | P | Y | 04/21/2022 | Y | N | 02/22/2018 | N | Y |
| Clark | Leslie | Study Coordinator | SP | Y | N | | P | Y | 02/26/2024 | Y | N | 05/14/2021 | N | Y |
| Collins | Heather | Study Coordinator | DP | Y | Y | RN, BSN | P | Y | 02/13/2024 | Y | N | 02/22/2018 | N | Y |
| Dang | Sumit | Co-Investigator | SP | Y | N | MD | P | Y | 03/27/2023 | Y | N | 02/22/2018 | N | Y |
| deGraaff | Susan | Project Assistance/Support | DP | N | Y | | P | Y | 11/03/2023 | Y | N | 05/05/2021 | N | Y |
| Desai | Jay | Sub-Investigator | SP | Y | N | MBBS | N | Y | 03/03/3000 | | N | 10/15/2024 | N | Y |
| Fletcher | Katherine | Project Assistance/Support | SP | Y | N | | P | Y | 08/23/2023 | Y | N | 02/22/2018 | N | Y |
| Giannone | Peter | Co-Investigator | SP | Y | N | MD | P | Y | 04/12/2023 | Y | N | 02/22/2018 | N | Y |
| Goldstein | Ricki | Co-Investigator | SP | Y | N | MD | P | Y | 07/12/2024 | Y | N | 02/22/2018 | N | Y |
| Grider | Deborah | Project Assistance/Support | SP | Y | N | RN | P | Y | 07/03/2024 | Y | N | 02/22/2018 | N | Y |
| Hanna | Mina | Co-Investigator | SP | Y | N | MD | P | Y | 11/11/2024 | Y | N | 02/22/2018 | N | Y |
| Henderson | Bradley | Project Assistance/Support | SP | N | N | PharmD | P | Y | 09/12/2023 | Y | N | 01/11/2021 | N | Y |
| Hobbs | Carrie | Study Coordinator | DP | Y | Y | RN, BSN | P | Y | 11/03/2023 | Y | N | 02/22/2018 | N | Y |
| Horn | Jamie | Project Assistance/Support | SP | N | N | | P | Y | 02/15/2022 | | N | 05/08/2018 | N | N |
| Huang | Hong | Data Analysis/Processing | SP | N | N | MD, PhD | P | Y | 07/28/2022 | Y | N | 02/22/2018 | N | Y |
| Larkin | Seth | Project Assistance/Support | SP | N | N | | P | Y | 10/24/2024 | Y | N | 02/22/2018 | N | Y |
| Lyman | Thomas | Project Assistance/Support | SP | Y | N | | P | Y | 06/09/2023 | Y | N | 02/22/2018 | N | Y |
| Mangino | Anthony | Co-Investigator | SP | N | N | PhD | P | Y | 11/01/2022 | Y | N | 12/16/2024 | N | Y |
| McKinney-Whitlock | Alisa | Project Assistance/Support | DP | N | Y | | P | Y | 02/13/2024 | Y | N | 02/22/2018 | N | Y |
| Olszewski | Ashley | Co-Investigator | SP | Y | N | | P | Y | 05/01/2024 | Y | N | 09/20/2019 | N | Y |
| Palla | Muralimohan | Co-Investigator | SP | Y | N | MD | P | Y | 05/10/2022 | N | N | 02/22/2018 | N | Y |
| Pijut | Sonja | Project Assistance/Support | SP | N | N | PharmD, PhD | P | Y | 01/04/2023 | N | N | 01/11/2021 | N | Y |
| Quire | Kimberly | Study Coordinator | DP | Y | N | | P | Y | 06/11/2024 | Y | N | 07/28/2021 | N | Y |

| Last Name | First Name | Responsibility In Project | Role | AC | Contact | Degree | StatusFlag | (HSP) | (HSP)Date | (RCR) | Removed? | Last Updated | SFI | Active |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schadler | Aric | Data Analysis/Processing | SP | N | N | | P | Y | 06/10/2024 | Y | N | 09/24/2018 | N | Y |
| Schanbacher | Brandon | Data Analysis/Processing | SP | N | N | | P | Y | 10/09/2023 | Y | N | 02/22/2018 | N | Y |
| Sithisarn | Thitinart | Co-Investigator | SP | Y | N | MD | P | Y | 12/08/2022 | Y | N | 02/22/2018 | N | Y |
| Slone | Alison | Co-Investigator | SP | Y | N | MD | P | Y | 11/08/2023 | Y | N | 02/22/2018 | N | Y |
| Spencer | Margaret | Project Assistance/Support | SP | N | N | CPhT | P | Y | 07/18/2023 | Y | N | 01/11/2021 | N | Y |
| Stratton | Ashley | Study Coordinator | SP | Y | N | | N | Y | 03/03/3000 | | N | 06/01/2021 | N | Y |
| Tang | Fei | Data Analysis/Processing | SP | N | N | | N | Y | 03/03/3000 | | N | 08/23/2022 | N | Y |
| Westgate | Philip | Co-Investigator | SP | N | N | | P | Y | 05/25/2023 | Y | N | 02/22/2018 | N | Y |
| Wilburn | Amanda | Project Assistance/Support | DP | Y | Y | | P | Y | 01/10/2022 | Y | N | 08/24/2021 | N | Y |
| Wood | Christopher | Project Assistance/Support | SP | N | N | RPh | P | Y | 05/31/2023 | | N | 01/11/2021 | N | N |
| Zapata | Stephanie | Project Assistance/Support | SP | N | N | CPhT | P | Y | 11/24/2023 | Y | N | 01/11/2021 | N | Y |
| Abu Jawdeh | Elie | Co-Investigator | SP | Y | N | MD | N | Y | 11/07/2023 | N | Y | 09/16/2024 | N | Y |
| Ajour | Maher | Co-Investigator | SP | Y | N | | P | N | 07/20/2020 | | Y | 12/04/2023 | N | N |
| Akhtar | Ahsan | Co-Investigator | SP | Y | N | MBBS | S | N | 07/20/2018 | | Y | 07/28/2021 | N | N |
| Amrit | Ellora | Data Analysis/Processing | SP | Y | N | | P | N | 12/06/2020 | | Y | 12/04/2023 | N | Y |
| Baker | Max | Project Assistance/Support | SP | N | N | | S | N | 08/13/2020 | | Y | 07/28/2021 | N | N |
| Bhavsar | Ravi | Co-Investigator | SP | Y | N | | P | Y | 11/15/2022 | Y | Y | 09/16/2024 | N | Y |
| Brasher | Mandy | Co-Investigator | SP | Y | N | | P | Y | 02/25/2023 | | Y | 11/27/2023 | N | N |
| Butler | Sara | Data Collection | SP | Y | N | RN, BSN | P | N | 03/13/2021 | | Y | 11/27/2023 | N | N |
| Caldwell | Rhonda | Sub-Investigator | SP | Y | N | PT | | Y | 06/20/2023 | Y | Y | 09/16/2024 | N | N |
| Cash | Morgan | Project Assistance/Support | SP | N | N | | S | N | 08/13/2020 | | Y | 07/28/2021 | N | N |
| Cohen | Shalonda | Project Assistance/Support | SP | Y | N | | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Deng | Pan | Data Analysis/Processing | SP | N | N | | P | N | 08/24/2020 | | Y | 12/04/2023 | N | N |
| Desai | Nirmala | Co-Investigator | SP | Y | N | MD | | N | 03/15/2021 | | Y | 09/16/2024 | N | N |
| Dowden | Carl | Co-Investigator | SP | Y | N | | P | N | 10/28/2019 | | Y | 12/04/2023 | N | N |
| Dowden | Lauren | Co-Investigator | SP | Y | N | | | Y | 03/08/2022 | | Y | 09/16/2024 | N | N |
| Dudhate | Ambika | Data Analysis/Processing | SP | N | N | | P | N | 05/21/2020 | | Y | 12/04/2023 | N | N |
| Dunworth | Caitlin | Data Collection | DP | Y | Y | MPH | P | N | 02/16/2021 | | Y | 01/24/2023 | N | N |
| Gaston | Piyamas | Sub-Investigator | SP | Y | N | PharmD | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Haase | Anthony | Co-Investigator | SP | Y | N | | P | Y | 05/08/2024 | Y | Y | 09/16/2024 | N | Y |
| Hargrove | Skylar | Data Analysis/Processing | SP | Y | N | | P | Y | 05/03/2022 | | Y | 12/04/2023 | N | Y |
| Hunter | Aaron | Project Assistance/Support | SP | N | N | PharmD, MSPS | P | Y | 05/18/2024 | Y | Y | 09/16/2024 | N | Y |
| Isaacs | James | Project Assistance/Support | SP | N | N | PharmD, MSPS | P | Y | 04/03/2024 | Y | Y | 09/16/2024 | N | Y |
| Kinison | Scott | Project Assistance/Support | SP | N | N | | P | N | 05/08/2020 | N | Y | 12/04/2023 | N | Y |
| Leggas | Markos | Co-Investigator | SP | N | N | PhD | P | N | 12/20/2016 | | Y | 05/11/2022 | N | N |
| Mahaffey | Bandi | Co-Investigator | SP | Y | N | | | N | 10/19/2021 | | Y | 10/29/2024 | N | N |
| Murphy | Laura | Project Assistance/Support | SP | Y | N | EdD | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Narayanan | Uma Priya | Project Assistance/Support | SP | N | N | | P | Y | 07/24/2022 | | Y | 09/01/2022 | N | Y |
| Ng | Chee Meng | Co-Investigator | SP | N | N | | P | N | 07/03/2018 | | Y | 01/26/2022 | N | N |
| Parchman | Bob | Project Assistance/Support | SP | N | N | | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Patra | Aparna | Co-Investigator | SP | Y | N | MD | P | N | 07/29/2020 | | Y | 12/04/2023 | N | N |

| Last Name | First Name | Responsibility In Project | Role | A C | Contact | Degree | StatusFlag | (HSP) | (HSP)Date | (RCR) | Removed? | Last Updated | SFI | Active |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Peery | Pat | Project Assistance/Support | SP | N | N | | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Phillips | Susan | Project Assistance/Support | SP | Y | N | | P | N | 02/21/2018 | | Y | 02/12/2021 | N | N |
| Piatek | Monika | Sub-Investigator | SP | Y | N | | P | N | 10/19/2018 | | Y | 07/28/2021 | N | N |
| Pollard | Leann | Data Collection | SP | Y | N | BS | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Pourcyrous | Massroor | Co-Investigator | SP | Y | N | MD | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Rana | Divya | Sub-Investigator | SP | Y | N | MD | N | Y | 03/03/3000 | | Y | 10/15/2024 | N | Y |
| Shearer-Miller | Jennifer | Sub-Investigator | SP | Y | N | PhD RN | N | Y | 09/23/2022 | | Y | 12/13/2023 | N | Y |
| Sitzlar | Stephen | Project Assistance/Support | SP | N | N | RPh, PharmD | P | N | 11/28/2018 | | Y | 01/11/2021 | N | N |
| Stacy | Audra | Sub-Investigator | SP | Y | N | | P | Y | 05/09/2024 | Y | Y | 09/16/2024 | N | Y |
| Stevens | Brandi | Project Assistance/Support | SP | Y | N | | | Y | 11/03/2023 | N | Y | 09/16/2024 | N | N |
| Struewing | Kaylee | Co-Investigator | SP | Y | N | | P | N | 07/29/2019 | | Y | 12/04/2023 | N | Y |
| Thakkar | Pratibha | Co-Investigator | SP | Y | N | MBBS | P | N | 11/28/2019 | N | Y | 11/27/2023 | N | N |
| Whitehead | Vicki | Study Coordinator | DP | Y | Y | RN | P | Y | 02/13/2024 | Y | Y | 01/24/2023 | N | Y |

**RESEARCH DESCRIPTION**

**0 unresolved comment(s)**

**You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.**

**Pro Tips:**

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

**Background**

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

The non-prescribed use of opiates as painkillers by pregnant women has become an emerging morbidity, with a higher prevalence than cocaine or methamphetamine use. In addition, neonates are exposed to opiates, such as methadone or buprenorphine, during treatment for maternal opiate addiction or dependence. The prescription opiates include oxycodone, hydrocodone, hydromorphone, propoxyphene, codeine, etc. Prenatal exposure to these drugs results in withdrawal manifestations or neonatal abstinence syndrome (NAS), not different from signs reported following prenatal exposure to heroin or methadone.5 Among infants with prenatal opiate exposure, the incidence of NAS ranges from 21% to 93% 6-11; with higher incidence following prenatal methadone exposure.12, 13 Approximately 50% of those with symptoms require pharmacological treatment. Also, most mothers who are drug dependent are also polydrug users, with concurrent use of one or more substances such as benzodiazepines, barbiturates, selective serotonin reuptake inhibitors, cocaine, marijuana, amphetamine or meth-amphetamine, and legal drugs such as tobacco and alcohol. Polydrug exposure is also associated with greater severity of withdrawal manifestations14 and increases the odds for a neonate to develop signs of NAS. In a large cohort, infants that were exposed prenatally to both opiate and cocaine were more likely to show signs of withdrawal than infants exposed to either drug alone6.

Recent reviews of published treatment strategies and surveys of practices among clinical centers indicate a variety of approaches to the pharmacological management of NAS. In fact, only 54.5% of centers in the US have a protocol in place for the management of NAS.2 It is general practice that an opioid is the first line therapy for NAS after prenatal opiate exposure.15 Indeed, 83% of US centers use some type of opioid for initial pharmacological treatment of NAS.2 An increasing number (92%) of the centers in the United Kingdom and Ireland16 also use opiates as first line drug compared to an earlier survey, wherein chlorpromazine was the most commonly used treatment (71% of centers). In polydrug exposure, opioids remain first line therapy in 52% of US centers, followed by phenobarbital in 32% and methadone in 11% of centers.2 A second (adjunctive) therapeutic agent may be added if control of symptoms is not achieved with the first drug.2 Adjunctive treatment may also decrease the severity of withdrawal symptomatology and the infant's length of hospital stay.17, 18 Examples of the drugs for use in conjunctions with the first line drug are phenobarbital, clonidine, methadone, diazepam and choral hydrate.

There is a lack of consensus on the dosage of opiate for NAS treatment, interval between dosing, what scoring system to use as a guide to initiate treatment, when to start weaning the dose after control of symptoms, and which and when an adjunctive drug should be used. In a recent Cochrane review, morphine appeared to be commonly used but evidence from large randomized trials is lacking.3 Long term outcomes following NAS treatment are unknown.

From our clinical experience we have observed that the symptoms of NAS may decrease in severity with opiate administration; however, there are both experimental and human studies that suggest detrimental effects of opiates on the developing brain. Depending upon the gestational stage during which an opioid is taken, gross malformations may be observed. Gross abnormalities in brain development have been reported in opiate-exposed infants, e.g., hydrocephaly with prenatal heroin19 and codeine exposures.20 We recently reported on neonatal stroke following prenatal codeine prescribed as anti-tussive during pregnancy.21 In human neonates, prenatal opiate exposure results in a 0.5 to 2 cm decrease in head circumference,22-28 proportional to the decrease in body size, i.e., symmetric growth restriction associated with decrease in cell number, and consistent with the findings of Naeye et al.,29 in heroin exposed fetuses at 30 weeks gestation. In animals, prenatal opioid or μ-receptor agonists exposure results in decreased cortical density of neurons, and smaller dendritic arborization and branching, therefore affecting programming of cortical structures.30-33 Early exposure to μ-agonists therefore might lead to decrease in neurogenesis in neocortex, limbic system and/or cerebellum, leading to decreased volumes of these brain regions and corresponding behavioral effects in overall cognition (isocortex), emotion and social interactions (limbic system), and motor learning and performance (cerebellum). These findings may explain the reported prenatal and postnatal head growth deceleration in the human newborn with prenatal opiate exposure.22-28, 34-37 Additionally, in ventilated preterm infants, morphine as an analgesia has been associated with an increased incidence of neurological complications such as intraventricular hemorrhage, not necessarily from direct effect of morphine, but perhaps from the hypotension following morphine administration.38, 39 Although recent report in newborns with prenatal opiate exposure showed no pathological findings on anatomical MRI,40 brain volumes were not measured. In older children, however, there is a suggestion of decreases in brain volumes among those with prenatal opiate exposure.41 There are also multiple effects reported on opiate as affecting the hypothalamic-pituitary axis, and the neonatal immunological response. Therefore, a non-opiate drug becomes attractive as an alternative to morphine treatment of NAS. The drugs phenobarbital, benzodiazepine, chlorpromazine, etc. are sedatives and their

action is not specific to the underlying pathogenesis in opiate withdrawal. Moreover, phenobarbital or benzodiazepines, acting by blockage of N-methyl -D-aspartate receptor-mediated excitation and as agonists to gamma aminobutyric acid (GABA) subtype A receptors, have been shown to impair cell proliferation and inhibit neurogenesis.42

In the original pilot trial, we selected clonidine as an alternative, since clonidine as an a-adrenergic agent, acts on the central sympathetic activity, which has been shown to be increased with opiate withdrawal. Prolonged opiate exposure results in activation of opiate receptors in the locus ceruleus, which contain clusters of noradrenergic cells. Opiate exposure decreases adenylate cyclase activity, reducing cAMP levels. 43-45 Such effect on cAMP results in an increase in potassium efflux with associated decrease in calcium influx; these processes are inhibitory to brain noradrenergic activity.46,47 With cessation of opiate supply, the inhibitory effect of chronic opiate on noradrenergic activity is lost resulting in increased noradrenergic activity.48 Clonidine, an a2 adrenoreceptor agonist has inhibitory effects on noradrenaline release in the locus ceruleus; its administration decreases noradrenergic neuronal activity and consequently decreasing withdrawal manifestations. Clonidine has previously been reported as a single drug therapy for NAS,49, 50 and recently as an adjunct to morphine.18 If administered with choral hydrate51 the duration of treatment for NAS is shorter compared to morphine plus phenobarbital. It has been used in neonates post operatively to prevent NAS.52 Because of the potential effects of continued opiate use on the developing brain, we propose to evaluate the use of clonidine in the treatment of NAS

In this current proposal, the research plan is based on our pilot study, 62 which randomized infants with NAS, >35 weeks' gestational age, to receive morphine (n=15) or clonidine (n=16). The treatment groups were similar as to mean birth weight, gestational age, Apgar scores, and postnatal age at treatment. Infants enrolled had no other medical or surgical complications. Treatment was initiated per our NICU standard at the time, and will be continued in this protocol. Total LOS was shorter by about 1 week in the clonidine (mean of 15 days), compared to 21 days in the morphine group. (See NIH protocol for additional information, page 3-4).

Addendum:
Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose.

**Objectives**

List your research objectives. Please include a summary of intended research objectives in the box below.

To determine whether the treatment of NAS with a non-opiate medication, clonidine, will be more effective than morphine
• Compare Clonidine and morphine for the treatment of NAS. Compare the efficacy of each drug which is determined by duration of treatment in number of days, number of dose escalations needed to achieve needed treatment, and the need for second drug treatment.

To determine whether treatment of NAS with clonidine will result in better early childhood outcomes than those treated with morphine

• Evaluate the neurobehavioral performance scores (habituation, orientation, self- regulation, motor/reflexes, and stress/ abstinence scales) using the neonatal intensive care (NICU) network neurobehavioral scale (NNNS) in both treatment groups. This exam will take place within the first few days after treatment begins and before discharge after study drug is discontinued.
• Compare the cognitive, motor and behavioral development of children in both treatment groups using the Bayley III Scales of Infant Development at 6 months, one and two years of age.

To build population pharmacokinetic/pharmacodynamic models and determine factors that affect exposure and response to morphine and clonidine
• Measure blood levels obtained at random times and correlate to Finnegan scores. The pharmacodynamics may help with understanding NAS medications and coping measures in babies.
• DNA extracted from cheek swabs in all four cohorts will be used to analyze single nucleotide polymorphisms (SNPs) and epigenetic modifications in select genes that have previously been demonstrated to have an effect either on the pharmacokinetics or efficacy of morphine and clonidine. These findings will be used as covariates in the PK/PD population model to develop a comprehensive and quantitative assessment of the overall significance individual or multiple SNPs play in the variability of length of hospital stay.

To determine whether NAS related pathophysiology affects the disposition and response to morphine and clonidine.
• Stool samples collected among babies treated for NAS (Cohort 1) will be used to study the effect of prenatal and/or perinatal opioid exposure on the development and phenotype of the microbiome, as altered microbiota are hypothesized to affect metabolism and disposition of NAS treatment drugs.

Data collection for non-treated and consented patients:
• Having samples and data collected from all four cohorts (treated NAS, non-treated NAS, and well babies NICU and non-NICU) will allow for further analysis and reveal any factors that might influence management of NAS symptoms and treatment in the future.

Addendum:
Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley

exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose.

Addendum-CBCL cohort:
This cohort DOES NOT include any new enrollments and will only be enrolling from the cohort of treated infants at UK. The objective of this modification is to continue long-term follow up via a one-time questionnaire from enrolled patients' families who have minimal follow up data. The CBCL is valid for children up to 5 years of age, which will allow for additional data analysis on patients who have very minimal data collected due to non-compliance with the protocol.

**Study Design**

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This study design is a multi-site double-blinded randomized clinical trial. Patients enrolled in this study will be designated to 1 of 4 cohorts depending on their exposure during utero, need for treatment, or lack thereof.
This study closed to enrollment in 2021 and includes only follow up and data analysis at this point.
Addendum- CBCL cohort
This part of the study is survey research. The Childhood Behavior Checklist (CBCL) is a standardized questionnaire for parents of children up to 5 years old about their behaviors and emotions. This questionnaire will be sent via RedCap.

Attachments

**Subject Recruitment Methods & Advertising**

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

The Kentucky Children's Hospital admits about 900 newborns a year, and in 2016 there were 170 diagnosed with Neonatal Abstinence Syndrome (NAS). Due to maternal history, many of these newborns are diagnosed at delivery with the potential for withdrawal symptoms, and develop actual NAS in the first few days. Babies that are born at referral hospitals are sent to the Kentucky Children's Hospital during the first week due to severity of symptoms. The co-investigators will be the attending physicians and fellows caring for these babies and will be aware of the enrollment criteria. Recruitment for well babies within cohort 3 will include patients in the Kentucky Children's Hospital that meet inclusion criteria with no exposure to opiates. Research coordinators are screening the patient census in these areas around the clock to ensure full capture of the individuals that qualify.

Regional One Health (including the University of Tennessee health Science Center) has around 3,200 deliveries a year with an average of three infants per month diagnosed with neonatal abstinence syndrome. Babies that are born at nearby referral hospitals are sent to the UTHSC during the first week of life due to severity of symptoms. UTHSC has committed to recruit approximately 40 of the already 1000 approved subjects.

Addendum:
A few selected caregivers who are already enrolled in the study will be approached during the regular time that their baby would be receiving a developmental assessment and asked if they would like to volunteer to allow their baby's assessment to be recorded. The video consent and purpose for the recording will be explained. Caretakers may decline to have their baby's developmental assessment recorded.

Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the

future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose.
A study flyer submitted to the IRB was approved 3/13/2018. This flyer is intended to be distributed to OB and maternal clinics, and in particular is to be distributed among UK Polk Dalton Pathways Program participants. The flyer was approved by UK Public Relations' Mallory Powell on 2/13/2018.

The NACU vs. study comparison chart is a laminated, visual chart placed in all 8 NACU rooms. This comparison chart is used as a visual tool for mothers at the bedside to be able to understand the difference between the standard of care in the NACU and patients enrolled in the No-Poppy study. They can visually see the extra procedures (i.e, blood samples, developmental test, and interview) required of patients enrolled in the study.

Addendum: CBCL cohort
The research team will contact the person who signed consent when the patient was enrolled in the study. We will only be recruiting from subjects in cohort 1, consisting of infants exposed to opiates while in utero and requiring pharmacologic treatment to treat their withdrawal symptoms. enrolled at UK. We will check the original consent and verify contact information via Epic. Patients' families will be contacted by phone using the number(s) given at time of consent. If family is interested in participating, they will be sent a survey invitation to their email address.

Attachments

| Attach Type | File Name |
|---|---|
| Advertising | Research Flyer NOPOPPYAPPROVED.pdf |
| Advertising | NACU_vs_Study_compared 11-29-18.pdf |

**Research Procedures**

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Initially, for an opiate-exposed neonate, behavioral care is started (quiet room, swaddling, ad lib feeding, vestibular movement). After an infant is admitted to Kentucky Children's Hospital with suspected NAS or at risk for NAS, standard care is to monitor for signs of withdrawal to determine the need for treatment. Currently, babies are prescribed an opiate replacement per medical provider discretion.

Cohort 1: After consenting, when the baby requires treatment, an order will be written to initiate treatment and the pharmacy will receive orders to randomize. The infant will be randomized to receive oral morphine or oral clonidine. Randomization will be done by Investigational Drug Services Unit (IDS) using computerized randomization. Kentucky Children's Hospital personnel administering the drug will be blinded to the treatment. Drug will be prepared and dispensed in similarly appearing solutions and volumes. Newborns requiring a second drug to help relieve the symptoms will be treated with either the opposite research medication being used and/or phenobarbital for both groups and at attending discretion.
Morphine Therapy:
If a baby is randomized to morphine, the starting dose is 0.06 mg/kg/dose (every 3 or 4 hours, depending on the feeding schedule). Dose will increase by 25% of initial dose every 12-24 hours until NAS scores are consistently <8 and symptoms are stable – up to 0.12 mg/kg/dose. (Once max dose of morphine is met, add second therapy - see "Second Therapy" section). Once stable on acceptable dose, the dose will remain unchanged (stabilization) for at least 24-48 hours with scores <8. Then weaning may begin - decrease by 10% of max dose every 24 hours, then continue wean pattern as tolerated. If necessary, baby may be weaned more frequently at physician's discretion. When total dose is 0.006mg/kg/dose and scores are <8 for 24 hours, change dosing to every 6 hours. If FS <8 for 24-48 hours, may discontinue morphine, continue to monitor for 48 hours, and then may discharge. If re-escalation is needed, the previous dose will be administered. If re-escalation is needed, the infant will begin weaning again on the above weaning schedule once the infant has had scores <8 for 24-48 hours on escalated dose.
Clonidine Therapy:
Babies randomized to clonidine will receive 1mcg/kg/dose (with a dosing interval of 3 or 4 hours, depending on the feeding schedule). This group will also receive increases by 25% of initial dose every 12-24 hours until NAS scores are consistently <8 and symptoms are stable – up to 2 mcg/kg/dose.(Once max dose of clonidine is met, add second therapy - see "Second Therapy" section). 50 The dose will remain unchanged for 24-48 hours once stable with scores <8. Then, dose will be decreased by 10% of max dose every 24 hours. If necessary, baby may be weaned more frequently at physician's discretion. When total dose reaches 0.1mcg/kg/dose and scores <8 for 24 hours, change dosing to every 6 hours. If FS <8 for 24-48 hours, may discontinue clonidine, continue to monitor for 48 hours, and then baby may be discharged. If re-escalation is needed the previous dose will be administered. If re-escalation is needed, the infant will begin weaning again on the above weaning schedule once the infant has had scores <8 for 24-48 hours on escalated dose.

Please see Appendix A for the Dosing Flowchart
Second Therapy:
Failure of primary research drug is defined as need for a second drug, secondary research drug and/or Phenobarbital, which would be added after maximum study drug dose failed to control NAS symptoms. The choice of which secondary therapy to start will be left up to the attending physician:

Adjunct Study Drug or Phenobarbital
Dosing based on study protocol Dosing based on standard of care
BOTH study drugs will remain blinded** Weaning is based on attending discretion
Weaning based on study protocol May be discharged on taper to be weaned at home
will be initiated AFTER primary drug has been discontinued
BOTH study drugs must be discontinued before discharge

Occasionally, babies undergoing treatment for NAS are discharged with a "drug taper". Babies enrolled in this study will not be sent home on study medication. Every effort will be made to keep that baby in the hospital, but if necessary, the study med will be stopped and the physicians will decide to either keep the baby on the randomized drug or change medication. The "go home" medication will be a known drug to the family, typically Phenobarbital, and NOT be paid for by the grant, since the study drug is terminated at discharge.

Biospecimen Collection:
Research labs will be drawn throughout the baby's hospital stay. An attempt will be made to draw additional samples when other labs are drawn, such as bilirubin and hematocrit levels, newborn state screen tests, etc., and from the same site as the ordered labs (i.e., a

heel stick, venous blood draw, etc).. The amount of blood is less than 1ml each time, and obtained up to 6 times during treatment for NAS. Drug levels, inflammatory markers and pharmacodynamics will be analyzed from these samples. The blood levels will not be used to adjust dosage, but to correlate the actual drug concentrations with the Finnegan Scores. The drug concentrations will be sent to a research lab, and will only be made available to the research staff after study completion to prevent unmasking of drug randomization. During hospitalization, infant's stool and saliva will be obtained periodically to analyze epigenetic modifications in select genes and DNA markers. The DNA markers may have an effect on the efficacy of the drug treatment

Developmental Assessments and Interviews:

The research team will perform an assessment within the first few days after treatment is initiated, using the NICU network neurobehavioral scale (NNNS)57. Examiners administering NNNS are trained and certified, and will be blinded to treatment received. A second NNNS exam will be performed when the infant has been weaned off of study medication before discharge. The secondary site at UTHSC will perform the NNNS-2 in lieu of the NNNS, this is a shortened version that has been tested for validity and reliability. Monitoring and data collection of clinical status while on the study will include documentation of interval FS, changes in dosing (increase, decrease, etc), observation for side effects such as drowsiness and apnea with either treatment, monitoring heart rate and blood pressure at least every 8 hours, until maximum dose is reached. Drug concentrations will be obtained at various times, depending on standard lab draws. Finnegan scoring will continue to be monitored after tapering of dosage has been started. Review and data collection of infant and maternal records will be done to obtain prenatal history, pregnancy history, and on-going medical history. When possible and prior to discharge, caretaker interview will be done for detailed substance use inventory during pregnancy (legal and illegal drugs, and medication) Addiction Severity Index, information to derive the Hollingshead's socio-economic status (SES) and tracking information, as well as paternal and neighborhood characteristics. However, while all attempts will be made to obtain a caretaker interview while the patient is in the hospital, this is an unpredictable and not always stable population and their presence at bedside is not always guaranteed. Discharge data collection will include infant discharge diagnosis and neonatal complications, Child Protective Services involvement, and discharge disposition.

Since NAS is an increasing problem, developmental follow-up is currently attempted in NAS patients that have been treated for NAS at the NICU follow up clinic as Standard of Care. A Bayley III scores at adjusted ages of 6-8, 12-14, and 22-26 months, interval medical history, Child Protective Services involvement, physical and neurological exam, anthropometric measurements, and blood pressure measurements will be collected at each visit. Additionally at the adjusted 6-8,, 12-14, and 22-26 month visits, we will update the SES information; do a maternal or caretaker interview of continuing drug use, Parenting Stress Index, brief symptom inventory, Beck Depression Inventory and the Infant Behavior Questionnaire (6mo visit) and the Early Childhood Behavior Checklist (CBCL) at 24mo visit. For study patients, there will be monetary assistance as described in #15 Payment section. Many of our parents/guardians drive 2 – 4 hour each way to attend a 3 hour appointment, often both parents accompany the child and that is an entire day taken off from work. Information and scores obtained during the clinic visits will be considered in the data analysis, since the items may have effects on or confound outcomes. Beginning March 2020, the NICU Graduate Clinic switched most follow-up appointments to telehealth and Bayley III exams were unable to be performed remotely. The clinic switched to using the Ages and Stages Questionnaire (ASQ-3) which can be performed over the telephone. Until the clinic returns to in-person Bayley assessments, the research team will collect developmental follow-up data at 6-8, 12-14, and 22-26 month visits from the ASQ-3 assessment gathered by the NICU Graduate follow-up clinic in lieu of the Bayley III exam. At this same time, many families felt uncomfortable coming to in-person visits (the 6-8month and 12-14 month Bayleys III, able to be performed by the study team at the CCTS outpatient clinic) and in the cases of missed in-person visits, the study team chose to obtain caretaker interviews by phone.

Cohort 2: If the family agrees to their child's participation in this study, but the baby's Finnegan scores do NOT require treatment, a limited number of data points and research samples will still be collected. Biological samples will include one blood sample, one stool sample, and one buccal swab with a purpose to analyze DNA and biomarkers in correlation with withdrawal symptoms. The research team will perform an assessment within the first few days of admission to the unit if treatment is not necessary using the NICU network neurobehavioral scale (NNNS). Examiners administering NNNS are trained and certified. When possible, caretaker interview will be completed while infant is inpatient. Patients within cohort 2 will also receive developmental follow-up for research purposes at the ages of 6, 12, and 24 months. These visits will take place in the Center of Clinical and Translational Sciences (CCTS) facilities located within the University of Kentucky Chandler Medical Center. The research team will perform the standardized Bayley III exam at adjusted ages of 6-8, 12-14, and 22-26 months. Along with these scores, interval medical history, Child Protective Services involvement, physical and neurological exam, anthropometric measurements, and vital signs will be collected at each visit. Additionally at the adjusted 6-8, 12-14, and 22-26 month visits, we will update the SES information; do a maternal or caretaker interview of continuing drug use, Parenting Stress Index, brief symptom inventory, Beck Depression Inventory and the Infant Behavior Questionnaire (6mo visit) and the Early Childhood Behavior Checklist (CBCL) at 24mo visit. For study patients, there will be monetary assistance as described in #15 Payment section. Information and scores obtained during the clinic visits will be considered in the data analysis, since the items may have effects on or confound outcomes. Beginning in March 2020, many families felt uncomfortable coming to in-person visits (the 6-8month and 12-14 month Bayley III exams, able to be performed by the study team at the CCTS outpatient clinic) and in the cases of missed in-person visits, the study team chose to obtain caretaker interviews by phone.

Cohort 3: This control cohort will be enrolled from the Newborn Nursery, typically only having admission for two to three days. If the family agrees to their child's participation in this study and the baby has not been exposed to opiates in utero, a limited number of data points and research samples may be collected, depending on staffing availability and coordinator discretion. Biological samples may include one blood sample, one stool sample, and one buccal swab with a purpose to analyze DNA and biomarkers for comparison to those babies in the studies that have been exposed to opiates in utero. The research team may perform an assessment before discharge using the NICU network neurobehavioral scale (NNNS). The secondary site at UTHSC will perform the NNNS-2 in lieu of the NNNS, this is a shortened version that has been tested for validity and reliability. Examiners administering the NNNS are trained and certified. No monetary assistance will be given due to their time in the study only being confined in the hospital.

Cohort 4: This control cohort will be enrolled from the Neonatal Intensive Care Unit in hopes of having multiple collections of stool samples/ a longer period of time for admission. If the family agrees to their child's participation in this study and the baby has not been exposed to opiates in utero, a limited number of data points and research samples will be collected. Biological samples will include up to four stool samples with a purpose to analyze DNA and biomarkers for comparison to those babies in the studies that have been

exposed to opiates in utero. No monetary assistance will be given due to their time in the study only being confined in the hospital.

Addendum: Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose. The video will be used for training purposes for the Kentucky Children's Hospital Office of Pediatric Research of research personnel. Any private health information will be kept entirely confidential and not shared outside the research and clinical care team. A benefit of video-taping the NNNS or Bayley developmental assessments is that this limits the number of "observers" at the infant's bedside. The video of the exam will not be used for any other purposes but for research training.

Should twins be enrolled in the study, both twins will be randomized to the same pharmacological treatment arm should they both need treatment. However, a case may occur when both twins are enrolled into the study, but do not both require pharmacologic treatment. If that is the case, only the twin requiring pharmacological treatment will receive it. A family may choose to only enroll a twin requiring pharmacological treatment.

Addendum: CBCL cohort
For already enrolled subjects who meet criteria listed in subject recruitment methods/privacy section, the study team will reach out to families (using contact info collected at time of consent) about completing a one-time questionnaire, the Child Behavior Checklist (CBCL). This questionnaire has been input into RedCap for survey collection. Subjects will be contacted via phone and if interested, will be emailed a link to the survey. Subjects will be given the same study ID as their original study ID to use to login to their specific survey link.

Attachments

| Attach Type | File Name |
|---|---|
| ResearchProcedures | ChildBehaviorChecklistCBCLForN (4).pdf |
| ResearchProcedures | NOPOPPYalgorithm_edited_7.25.19.pdf |

**Data Collection & Research Materials**

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Please see attached Research description data collection_study activity table

Addendum: Due to restrictions with the outbreak of COVID-19 and the expectation that there will be further limitations for visitors to the NICU in the future, we are limiting the number of personnel directly interacting/observing the enrolled subjects. We will be obtaining consent from 8 caretaker/baby dyads to videotape the developmental assessments of their baby. There will be 2 videoed recordings (2 caretaker/baby dyads) for each developmental assessment (2 NNNS recorded, 2 6-month Bayley exams recorded, 2 12-month Bayley exams recorded, and 2 24-month Bayley exams recorded). The videotapes will be used to train new study personnel only. This method will help limit direct contact with subjects. We will use a separate video consent for this purpose.

Addendum: CBCL cohort
The CBCL is used as a developmental assessment by providers per standard of care. UK's NICU grad clinic uses the CBCL when indicated at 24 months. The CBCL was included in the 24M follow-up for this study, but is able to be used for children up to 5 years of age.

Attachments

| Attach Type | File Name |
|---|---|
| DataCollection | UpTo5YearCBCL_NOPOPPY.pdf |
| DataCollection | MailingInformationForCBCLParti.pdf |
| DataCollection | No Poppy REDCap project.pdf |
| DataCollection | Well baby infant demographics data collection form.pdf |
| DataCollection | Data collection study activity table 1-7-21.pdf |
| DataCollection | Order of Maternal Interviews.docx |
| DataCollection | No-POPPY Study Blood Collection Information Sheet.pdf |

**Resources**

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

All subjects will be patients in the Kentucky Children's Hospital. The Key Personnel list includes research coordinator(s), research nurses, case manager, Transport Team and the NICU medical care team (attending, fellows). The nursing staff is experienced in caring for NAS infants – in 2016 there were over 230 babies admitted (not all required treatment) that were born to drug addicted mothers. The Finnegan scoring system is done routinely although the nurses will be reinstructed (start of study and every six months) on the administration of the Finnegan Scoring to maintain consistency. Research personnel have been trained to perform the NNNS, by a study consultant. The study personnel also performs the Bayley-III assessment in the NICU Graduate Clinic. Research personnel and the Study Case Worker have been trained by an additional study consultant, in the administration of questionnaires, to ensure that questionnaires are administered appropriately, whether the questionnaires are structured, semi-structured, or non-structured. REDCap data management system will be used on the University's secure network, and data analysis will be conducted by Dr. Phillip Westgate and Dr. Richard Charnigo of the Department of Biostatistics and Epidemiology of the College of Public Health. All research data will be confidential and subjects identified only by ID number. We will comply with IRB regulations and HIPAA standards. We have obtained a certificate of confidentiality from NIH to give assurance to caretakers (mothers) the interview responses and research data will be held confidential and no reporting to legal authorities will be done except when in cases of suspected child abuse/neglect and harm to self or others.

The secondary site, UTHSC, those enrolled will all be patients in the University of Tennessee Health Science Center, which is part of Regional One Health. The UTHSC Key Personnel list includes research coordinator(s), research nurses, case manager, and the NICU medical care team (attending, fellows). The UTHSC key personnel will have their human subjects protection training kept on file both at UTHSC and UK. Although the UTHSC IRB is not reviewing the study, that IRB still routinely checks for that key personnel's training to ensure it remains up-to-date.

UTHSC will follow UK IRB's SOP for reporting and submitting unanticipated problems, noncompliance, AE's and SAE's. The Standard Operating Procedure document has been shared. UK's lead study team will be responsible for reporting all incidences to UK IRB and the study's DSMB. The Communication Plan Form has been uploaded under "Additional Information".

Biospecimen samples could be sent to St. Jude Children's Research Hospital (Department of Pharmacy and Pharm. Sciences 262 Danny Thomas Place, Memphis TN 38105) with the move of our Co-Investigator, Mark Leggas, MD. All biospecimen samples will be de-identified with the subject's study identification code.

Jennifer Shearer-Miller is a co-investigator and will assist with data analysis using de-identified subject information. She completed a post-doc fellowship at UK under Dr. Bada and is now employed at the University of Tennessee.

**Potential Risks & Benefits**

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

For this protocol, the risk of either treatment drug includes sleepiness, drowsiness, low blood pressure, low heart rate, constipation, and vomiting, sweating, or even apnea. However, with the dosage proposed based on studies in the literature, and results of the pilot study, we anticipate minimal risks to the subjects.
Risks associated with phlebotomy for the routine blood draws are bleeding, infection, bruising, and also pain. The heel sticks or intravenous sticks are usually done quickly so pain is likely only for a few seconds. Every effort is made to ensure these samples are done at the time of other labs, so the study samples will not aggravate or increase the risk that would normally occur. The two additional research blood draws carry the same risks as if they were being done as standard of care. Psychological and social risks may come up during interviews with substance abusing mothers, but this risk would be the same if they were not part of the study. Breach of Confidentiality is also a possible risk; all information will be maintained with the utmost confidentiality to ensure patient's privacy and protection and will only be shared with authorized research personnel. Data will be de-identified and assigned a unique identifier. A key

linking the unique identifier with the patient's PHI will be stored separately from the data in the locked office of the Research Coordinator (HA 1266, 800 Rose Street).

At UTHSC, a key linking the unique identifier with the patient's PHI will be stored separately from the data in the locked office of the Research Coordinator (853 Jefferson Avenue, Suite 201, Memphis, TN 38163).
In the case of any drug study, if the alternative non-opiate drug is beneficial, efficacious, or if proven superior to morphine, then practice will likely change. The risks of each drug currently used are basically the same, and the benefit hinted at in the pilot study may or may not be determined in this study. If this larger trial shows the expected benefit and/or improved outcomes this could possibly change or add to current practice.

Addendum:
The video of assessments will allow us to limit the number of study team members who come in physical contact with participants in the NICU.

**Available Alternative Opportunities/Treatments**

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

Infants with a diagnosis of NAS are currently treated in the Kentucky Children's Hospital with opiate replacement therapy. Due to the high number of NAS at UK, other protocols are being developed to improve standard of care such as darkened rooms, tight bundling, ad lib feedings and a core group of nurses to provide stable care. All of these measures will be instituted with this protocol. The only other available treatments include morphine and buprenorphine, with addition of secondary medications as needed – this would be the alternative to research.

Similar alternative treatments, and additional non-pharmacological treatments, are utilized at UTHSC as standard of care.

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**Records, Privacy, and Confidentiality**

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Most of the data collected will be information that is available in the electronic medical record, both infant and maternal, and during the interviews with the caretaker. Each patient enrolled will be assigned a unique identification number. The master list of patient names, MR#, and unique identifiers will be maintained in the neonatology research coordinator's office (HA 1266, 800 Rose Street) which is locked when not occupied. Patient data information will be obtained upon being enrolled in the study and continuously while on study medication or during length of stay. Research data information will only be viewed by the study personnel and all study documents will be labeled with unique identifiers only.
Other outcome measures include: neonatal performance on the NNNS within first few days post initiation of treatment or after admission, and 4 weeks post-natal (38-44 weeks) or discharge, drug levels in blood at various times or blood DNA levels if not requiring treatment (the levels will not be available until after study is complete), and 6-8, 12-14, and 22-26 months Bayley III Developmental Assessment scores.

For the UTHSC site, the master list of patient names, MR#, and unique identifiers will be maintained in the neonatology research coordinator's office at the University of Kentucky Children's Hospital (HA 1266, 800 Rose Street) and the University of Tennessee Health Science Center (853 Jefferson Avenue, Suite 201, Memphis, TN 38163) which is locked when not occupied.

Addendum:
The assessment videos will be not contain or be linked to any PHI outside of the unique study ID given to the subject. The video will be stored on the encrypted research drive on the firewall protected servers provided by the Kentucky Children's Hospital and will be used to teach new study personnel. KCH computers are password-protected.
Information about the study subjects will be maintained confidential throughout, and all identifiers will be purged after data collection. The infant's name will never appear in any publication or be mentioned in any public place in connection with this study. In all records of this study, the subject will be identified by a
study number, and their names will be known only to researchers. The list of study numbers and subject names will be kept in the research office. This office is locked when personnel are not present, and the files are only accessible by the PI and research personnel.

Data will be entered into a password-protected database REDCap, which is maintained on a protected server. Once entered in a password protected electronic file, the data will be de-identified for all subsequent analysis. The consents will be maintained in the research office until six years after closing the study with the IRB. Data and electronic records will also be kept for at least six years post study closure. When and if data and electronic records are destroyed it will be according to UK Policy A13-050.

The study team will work with the UK CCTS to gain REDCap access for the UTHSC study personnel.

Parents will be asked to provide personal contact information (on separate sheet) and social media account names in order to contact them on follow-up appointments. The NO-POPPY study has a private Facebook page. We may use this account to reach out to caregivers through private message to remind them of dates and times of clinic visits. An example of this private message may be, "Hello, this is a research associate from the University of Kentucky reminding you of your upcoming appointment with the NICU graduate clinic on Tuesday at 11:00am. During this appointment, there will be research activities such as developmental assessments and caretaker interviews to complete. We will also bring your travel reimbursement and gift card to this appointment. Please let me know as soon as you can if you need to reschedule." With this form of communication, we plan to minimize risk of breeching confidentiality by only direct messaging study participants, and by not choosing to "friend" them or creating a group to show everyone that is in said group.

Addendum:
The assessment videos will be not contain or be linked to any PHI outside of the unique study ID given to the subject. The video will be stored on the encrypted research drive on the firewall protected servers provided by the Kentucky Children's Hospital and will be used to teach new study personnel.
Newborns diagnosed with NAS in the Kentucky Children's Hospital are quite common and the current treatment with opiates has not resulted in any of the potential side effects. However unlikely, any serious and unexpected adverse event will be reported to the IRB according to current protocol. All babies will be monitored at all times as per protocol. Heart rate and blood pressure will be recorded at least every 8-12 hours, until maximum dose is reached; continue routine FS monitoring after tapering of dosage has been started. All subjects will be carefully monitored. Steps will be taken to assure confidentiality. De- identified patient data will be stored in REDCap on the central servers at Kentucky Children's Hospital and used for analysis. Individual data collection will be password protected and only the research staff and investigator will have access to those files. Unique identifiers will be used and PHI will be securely protected and stored separately from the data, in the locked office (HA 1266, 800 Rose Street) of the Research Coordinator. Paper containing PHI will be disposed of once the information is coded and no longer necessary for obtaining the required study information in a manner which meets HIPAA compliance and approved by the University of Kentucky Medical Center. In the event of publication of finding, all information to be presented in the literature will not breach confidentiality and participants will remain anonymous.

At UTHSC, de-identified patient data will be stored in REDCap on the central servers at University of Tennessee Health Science Center and used for analysis. Individual data collection will be password protected and only the research staff and investigator will have access to those files. Unique identifiers will be used and PHI will be securely protected and stored separately from the data, in the locked office (853 Jefferson Avenue, Suite 201, Memphis, TN 38163) of the Research Coordinator. At the UTHSC site, paper containing PHI will be disposed of once the information is coded and no longer necessary for obtaining the required study information in a manner which meets HIPAA compliance and approved by the University of Tennessee Health Science Center. In the event of publication of finding, all information to be presented in the literature will not breach confidentiality and participants will remain anonymous.

Addendum:
The assessment videos will be not contain or be linked to any PHI outside of the unique study ID given to the subject. The video will be stored on the encrypted research drive on the firewall protected servers provided by the Kentucky Children's Hospital and will be used to teach new study personnel. KCH computers are password-protected.

Addendum: CBCL cohort
The CBCL data collected will be connected to the patient's pre-existing study ID. When study staff sends the invitation to complete the survey, they will enter the study ID so that only that survey is attached the correct study ID. No PHI will be collected as part of this questionnaire. Additionally, to protect subject and caregiver privacy, a waiver of signatures is being requested since the patient's identity is already coded.

☑ **UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Check this item to confirm that you will retain all IRB-related records for a minimum of 6 years after study closure.**

**Payment**

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

No financial inducements are offered for patients to participate in this trial. All routine patient care charges will be billed to the patient or insurer accordingly. The study medications and the research related procedures (see table in "Research Procedures") are paid for from a research grant sponsored by NIH. If the patient is discharged on medication, the family is then responsible for prescription costs of the drug. Families will be given cash or pre-loaded gift cards at various intervals to cover travel costs (calculated per state mileage reimbursement rate), time away from work, parking, meals and other inconveniences per the following schedule:
Visit Amount
Baby's Discharge $25.00
Any clinical visit to
NICU graduate clinic $25.00
6 months * $50.00
1 year * $75.00
2 year * $100.00
*Round trip mileage reimbursement will also be included for each visit attended at the NICU Graduate Clinic.
Participants of Cohort 3 and 4 will not receive any travel reimbursement funds considering that their involvement in the study is confined to their time as a patient in the hospital.

Participants at UTHSC will receive a flat rate of $50.00 cash to cover travel costs, time away from work, parking, meals and other inconveniences. Mileage reimbursement will not be included with UTHSC due to the urban population verses UK's rural population.

Participants who complete the CBCL survey will be mailed a check for $75.00 within 3 business days of survey completion. After completing the survey, an automated email will be sent out through RedCap that will take participants to a separate RedCap survey to input their mailing information (see this survey in data collection section). This is not attached to their survey response and will be used only for payment.

**Costs to Subjects**

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

All routine patient care charges will be billed to the patient or insurer accordingly. All research related procedures outlined in the table under #7 (Research Procedures) are paid for from a research grant sponsored by NIH.

**Data and Safety Monitoring**

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

Monitoring for adverse events will be conducted in real-time by the study investigators and study coordinators. Risks involved with this study are considered greater than minimal risk. For this reason, we will utilize the standing independent Data Safety Monitoring Board (DSMB) as chartered by the University of Kentucky Center for Clinical and Translational Science (CCTS) to monitor the safety of this study.

The DSMB is an independent multidisciplinary group with clinical research experience representing relevant specialties. This group will include a Research Subject Advocate (RSA) who is a Physician, a Pharmacist, an Internal Medicine Physician, Statistician, CCTS Representative and Executive Secretary. Ad-hoc members may be added when experience in specific disease areas or procedures is required.

The DSMB will meet tri-annually or as needed, and will review subject recruitment, AE's, side effects, withdrawals, protocol violations, and inclusion/exclusion criteria related to Cohort 1 since it is the only cohort to receive pharmacological intervention.

Per the DSMB's request, an interim analysis will be conducted within the first year of subject recruitment. This safety analysis will be conducted by a non-study affiliated biostatistician and DSMB member, and will examine group differences, should any exist, between subjects receiving morphine or clonidine and their requirement of secondary treatment.

The UK CCTS DSMB will also be overseeing the secondary site, UTHSC.

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**Future Use and Sharing of Material (e.g., Data/Specimens/Information)**

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

Not applicable

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

**Recruitment and Consent:**

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

**Cultural and Language Consultants:**

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

**Local Requirements:**

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

**HIV/AIDS Research:** There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

**PI-Sponsored FDA-Regulated Research**

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

**HIPAA**

**0 unresolved comment(s)**

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

I have attached a HIPAA Waiver of Authorization. ○ Yes ◉ No

Attachments

## STUDY DRUG INFORMATION

**0 unresolved comment(s)**

**The term drug may include:**

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

**Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?**

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

**LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW**

Drug Name:

Clonidine
Morphine

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

**Is the study being conducted under a valid Investigational New Drug (IND) application?**

○ Yes ◉ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

**Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.**

Attachments

| Attach Type | File Name |
|---|---|
| Study Drug Form | complete_Form O_Clonidine.pdf |
| Study Drug Form | complete_Form O_morphine.pdf |
| Study Drug Form | CLONIDINE package insert approved with initial review.pdf |
| Study Drug Form | MORPHINE package insert approved with initial review.pdf |

## STUDY DEVICE INFORMATION

**0 unresolved comment(s)**

**A DEVICE may be a:**

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

**Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?**

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer "no" above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor's authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) being tested in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices being tested in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

**Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.**

Attachments

**RESEARCH SITES**

**0 unresolved comment(s)**

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☐ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☑ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky (UK) or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK sites.

- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

A secondary location where research will be located is the University of Tennessee Health Science Center (UTHSC), located at 853 Jefferson Avenue, Memphis, TN 38163. The University of Kentucky will be the lead site, and the UK IRB will be the reviewing IRB for the UTHSC site. Please see the attached letter of support.

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Biospecimen samples will be sent to co-investigator Mark Leggas at St. Jude Children's Hospital. Samples will be de-identified and a MTA will be established once IRB approval is received.

Please describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

Attachments

| Attach Type | File Name |
|---|---|
| -Individual Investigator Agreement | UK_Leggas_signed DUA.pdf |
| -Individual Investigator Agreement | MOU Leggas - Signed Treasurer.pdf |
| -IRB Authorization Agreement | StJude_IRB_Letter_ExemptStatus.pdf |
| -Letter of Support & Local Context | 19_3181 Signed Subrecipient Commitment Form to University of Kentucky.pdf |
| -Letter of Support & Local Context | UTHSC Local Context Information 20200121.pdf |

B) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

**RESEARCH ATTRIBUTES**

**0 unresolved comment(s)**

**Instructions: For various reasons, it is necessary to determine whether your research activities meet the definition of clinical research and/or a clinical trial. Your responses to the next series of questions will make that determination.** For more details on the definitions, go to ORI's clinical research vs. clinical trial web page or visit NIH's decision tree for the NIH Clinical Trial definition.

My research activities include one or more of the following:

Patient-oriented research regarding mechanisms of human disease, therapeutic interventions, clinical studies, or development of new technologies
◉ Yes ○ No

Material of human origin (such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects
◉ Yes ○ No

Epidemiologic or Behavioral Studies
○ Yes ◉ No

Outcomes Research or Health Services Research
○ Yes ◉ No

Does your research involve one or more human subjects prospectively assigned into one or more health-related biomedical or behavioral interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes?
◉ Yes ○ No

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

☐ Academic Degree/Required Research
☑ Alcohol/Drug/Substance Abuse Research
☐ Biological Specimen Bank Creation (for sharing)
☐ Cancer Research
☑ CCTS-Center for Clinical & Translational Science
☑ Certificate of Confidentiality
☐ Collection of Biological Specimens for banking and use
☐ Community-Based Participatory Research
☐ Deception
☐ Educational/Student Records (e.g., GPA, test scores)
☐ Emergency Use (Single Patient)
☐ Gene Transfer
☑ Genetic Research
☐ NIH Genomic Data Sharing (GDS) (databases such as GWAS, dbGaP, GenBank)
☐ Treatment with Human Cells, Tissues, and Cellular and Tissue Based Products
☐ Individual Expanded Access or Compassionate Use
☐ International Research
☐ Planned Emergency Research Involving Exception from

For additional requirements and information:

- Cancer Research (MCC PRMC)
- Certificate of Confidentiality (look up "Confidentiality/Privacy...")
- CCTS (Center for Clinical and Translational Science)
- Clinical Research (look up "What is the definition of....)
- Clinical Trial
- Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
- Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
- Community-Based Participatory Research (look up "Community-Engaged...")
- Data & Safety Monitoring Board (DSMB)

  *For Medical IRB: Service Request Form for CCTS DSMB

- Data & Safety Monitoring Plan
- Deception*

  *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
- Genetic Research (look up "Specimen/Tissue

Informed Consent

- ☐ Recombinant DNA
- ☐ Registry or data repository creation
- ☐ Stem Cell Research
- ☐ Suicide Ideation or Behavior Research
- ☑ Survey Research
- ☐ Transplants
- ☐ Use, storage and disposal of radioactive material and radiation producing devices
- ☐ Vaccine Trials

Collection...")

- Gene Transfer
- HIV/AIDS Research (look up "Reportable Diseases/Conditions")
- Screening for Reportable Diseases [E2.0000] (PDF)
- International Research (look up "International & Non-English Speaking")
- NIH Genomic Data Sharing (GDS) Policy (PDF)
- Planned Emergency Research Involving Waiver of Informed Consent*

*For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Use, storage and disposal of radioactive material and radiation producing devices

**FUNDING/SUPPORT**

**0 unresolved comment(s)**

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

☐ Grant application pending
☑ (HHS) Dept. of Health & Human Services
☑ (NIH) National Institutes of Health
☐ (CDC) Centers for Disease Control & Prevention
☐ (HRSA) Health Resources and Services Administration
☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
☐ (DoJ) Department of Justice or Bureau of Prisons
☐ (DoE) Department of Energy
☐ (EPA) Environmental Protection Agency
☐ Federal Agencies Other Than Those Listed Here
☐ Industry (Other than Pharmaceutical Companies)
☐ Internal Grant Program w/ proposal
☐ Internal Grant Program w/o proposal
☐ National Science Foundation
☐ Other Institutions of Higher Education
☐ Pharmaceutical Company
☐ Private Foundation/Association
☐ U.S. Department of Education
☐ State

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Other:

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

NIH/NIDA

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

| Attach Type | File Name |
|---|---|
| GrantContract | 3942049_Egrant.pdf |

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

| Attach Type | File Name |
|---|---|
| Funding_ProcessDODSOP | SOPadditional-protections-for-children.pdf |

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

## OTHER REVIEW COMMITTEES

**0 unresolved comment(s)**

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

**Additional Information**

- ☐ Institutional Biosafety Committee
- ☐ Radiation Safety Committee
- ☐ Radioactive Drug Research Committee
- ☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
- ☐ Graduate Medical Education Committee (GME)
- ☐ Office of Medical Education (OME)

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

**ADDITIONAL INFORMATION/MATERIALS**

**0 unresolved comment(s)**

Do you want specific information inserted into your approval letter? ◉ Yes ○ No

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

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Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

☐ Detailed protocol
☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
☑ Other Documents

Protocol/Other Attachments

| Attach Type | File Name |
|---|---|
| Other | Individual Investigator Agreement_Fei Tang.pdf |
| Other | Fei Tang HSP.pdf |
| Other | JHorn.HSR.pdf |

NOTE: [Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

**If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.**

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

**SIGNATURES (ASSURANCES)**

**0 unresolved comment(s)**

**Introduction**

All IRB applications require additional assurances by a Department Chairperson or equivalent (DA), and when applicable, a Faculty Advisor or equivalent (FA). This signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. The person assigned as DA *should not* also be listed in the Study Personnel section, and the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, refer to "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

**For a detailed illustration of how to complete this section, please review the short online video tutorial "Signatures (Assurance) Section - How to Complete," Otherwise, follow the steps below.**

## Required Signatures:

**Individuals chosen as signees may remove the application from their Inbox without signing the Assurance Statement by clicking "Return to PI" with a comment about why it is being returned (e.g., specific edits are deemed necessary).**

**The PI, and personnel chosen as a contact, will receive an email notification that edits are needed, and can find the draft application in both the "Draft" folder and the "Signatures Needed" folder located in the menu in the left margin of the default Inbox page. The researcher does not have a 'reply' option to the signee's comments and must make the requested edits directly in the application, or communicate outside the E-IRB system as to why not. Once the response is finalized, the researcher must re-visit the "Assurances Required" section to click the "Return to Signee" button for their re-consideration; the signee will receive an email notification at that time.**

**Hover your mouse cursor here for additional instructions.**

| First Name | Last Name | Role | Department | Signee Return Comment | Date Signed | |
|---|---|---|---|---|---|---|
| Henrietta | Bada | Principal Investigator | Pediatrics | | 03/23/2018 12:23 PM | View/Sign |
| Scottie | Day | Department Authorization | Pediatrics | | 03/22/2018 08:45 PM | View/Sign |

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

**Department Authorization**

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

**SUBMISSION INFORMATION**

**0 unresolved comment(s)**

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed. Otherwise your submission for IRB review and approval cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and you will receive a message to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Your protocol has been submitted.

Download all

| | Document Type | File Loaded | Document Description | File Size | Modified By | Mod Date |
|---|---|---|---|---|---|---|
| | ApprovalLetter | ApprovalLetter.pdf | | 0.083 | klars2 | 12/18/2024 8:12:08 AM |
| | DataCollection | MailingInformationForCBCLParti.pdf | Mailing Information Survey for CBCL Cohort | 0.032 | amwi284 | 2/27/2024 1:49:38 PM |
| | DataCollection | UpTo5YearCBCL_NOPOPPY.pdf | CBCL Only RedCap Project V1.2 | 0.078 | amwi284 | 2/27/2024 1:46:06 PM |
| | ResearchProcedures | ChildBehaviorChecklistCBCLForN (4).pdf | RedCap Project for CBCL cohort_updated | 0.079 | amwi284 | 2/21/2024 12:42:12 PM |
| | AddInfoProduct | JHorn.HSR.pdf | (Non-UK) Jamie Horn HSP | 0.075 | amwi284 | 12/4/2023 3:16:53 PM |
| | AddInfoProduct | Fei Tang HSP.pdf | Fei Tang_Non-UK Personnel HSP Training Certificate | 0.084 | amwi284 | 8/25/2022 2:38:48 PM |
| | AddInfoProduct | Individual Investigator Agreement_Fei Tang.pdf | Individual Investigator Agreement_Fei Tang | 0.864 | amwi284 | 8/25/2022 2:37:58 PM |
| | AdditionInfoConsiderations | Memo for #33 modification.pdf | Memo to IRB regarding control consent attachment | 0.068 | amwi284 | 5/16/2022 10:26:55 AM |
| | -Individual Investigator Agreement | UK_Leggas_signed DUA.pdf | DUA Leggas | 0.714 | amwi284 | 5/5/2022 11:35:38 AM |
| | -IRB Authorization Agreement | StJude_IRB_Letter_ExemptStatus.pdf | IRB Exempt Status - St. Jude | 0.072 | amwi284 | 5/5/2022 11:35:10 AM |
| | -Individual Investigator Agreement | MOU Leggas - Signed Treasurer.pdf | St. Jude - Leggas MOU | 4.866 | amwi284 | 5/5/2022 11:32:11 AM |
| | AdditionInfoConsiderations | FW_ NO-POPPY IRB question_1.pdf | PI response to Reliance | 0.261 | jato226 | 2/16/2022 9:50:42 AM |
| | AdditionInfoConsiderations | FW_ NO-POPPY IRB question.pdf | Reliance Discussion - UTHSC enrollment complete | 0.259 | jato226 | 2/10/2022 1:14:38 PM |
| | AdditionInfoConsiderations | Contact Information and Tracking sheet.pdf | Contact information and tracking sheet, email address added | 0.103 | cedu229 | 1/22/2021 9:33:23 AM |
| | DataCollection | No Poppy REDCap project.pdf | REDCap project 1-22-2021 | 1.271 | cedu229 | 1/22/2021 8:51:48 AM |
| | DataCollection | Data collection study activity table 1-7-21.pdf | Data collection table different cohorts vs. SOC | 0.077 | cedu229 | 1/7/2021 12:19:56 PM |
| | DataCollection | Well baby infant demographics data collection form.pdf | Control group data collection form | 0.040 | cedu229 | 1/7/2021 11:59:05 AM |
| | AdditionInfoConsiderations | Video Release Update 8.26.2020 bmw.docx | | 0.014 | cedu229 | 8/26/2020 8:45:21 AM |
| | AdditionInfoConsiderations | NoPOPPY UT IRB approval thru 3-18-21.pdf | UTHSC"s IRB approval through March 2021 | 1.110 | cedu229 | 8/20/2020 9:42:24 AM |
| | AdditionInfoConsiderations | 43976 Bada NO POPPY IAA UK-UTK-fullyexecuted7.13.2020.pdf | IAA UK-UTK | 0.251 | cedu229 | 7/13/2020 2:53:34 PM |
| | AdditionInfoConsiderations | SCOPE OF WORK from SRAS.pdf | Scope of Work from SRAS | 0.378 | cedu229 | 2/13/2020 3:40:28 PM |
| | AdditionInfoConsiderations | UTHSC combined logs (templates).pdf | Logs to be completed by UTHSC | 0.410 | cedu229 | 2/13/2020 2:58:44 PM |
| | AdditionInfoConsiderations | Completed UTHSC CVs Med Lic FD and GCP log - Template option 1 (version 021918).xlsx | HSP training log for UTHSC site | 0.188 | cedu229 | 2/13/2020 2:55:18 PM |
| | AdditionInfoConsiderations | UK communication plan.pdf | UK communication plan | 0.282 | cedu229 | 2/13/2020 1:13:25 PM |
| | -Letter of Support & Local Context | UTHSC Local Context Information 20200121.pdf | | 0.674 | cedu229 | 2/12/2020 2:09:37 PM |

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|---|---|---|---|---|---|---|
| -Letter of Support & Local Context | 19_3181 Signed Subrecipient Commitment Form to University of Kentucky.pdf | Letter of support UTHSC and UK | 1.322 | cedu229 | 2/12/2020 2:08:42 PM |
| AdditionInfoConsiderations | UK Relying Site Survey.pdf | UTHSC/UK Relying Site Survey | 0.196 | hlmurr2 | 2/6/2020 10:57:59 AM |
| AdditionInfoConsiderations | Tennessee Code Annotated and Research.pdf | Tennessee Code Annotated (TCA) and Human Subject Research | 0.190 | hlmurr2 | 2/6/2020 10:56:31 AM |
| AdditionInfoConsiderations | SOP informed-consent.pdf | UTHSC SOP informed consent (2) | 0.165 | hlmurr2 | 2/6/2020 10:55:28 AM |
| AdditionInfoConsiderations | NO-POPPY UT Reliance - Bada - FULLY Executed SMART IRB LoA and Supp Agreement.pdf | UK/UTSHC Reliance Agreement | 0.710 | hlmurr2 | 2/6/2020 10:54:37 AM |
| AdditionInfoConsiderations | C3-0050-Informed_Consent SOP for UK.pdf | UTHSC SOP for informed consent | 0.089 | hlmurr2 | 2/6/2020 10:54:13 AM |
| Funding_ProcessDODSOP | SOPadditional-protections-for-children.pdf | UTHSC- SOP for children | 0.143 | hlmurr2 | 2/4/2020 12:14:33 PM |
| StudyDrug | MORPHINE package insert approved with initial review.pdf | | 0.459 | hlmurr2 | 2/3/2020 10:48:45 AM |
| StudyDrug | CLONIDINE package insert approved with initial review.pdf | | 0.453 | hlmurr2 | 2/3/2020 10:48:34 AM |
| ResearchProcedures | NOPOPPYalgorithm_edited_7.25.19.pdf | Updated Algorithm to align with protocol for research medication | 0.129 | clburk4 | 9/20/2019 2:40:30 PM |
| StudyPopulation | breakdown chart of study population.pdf | | 0.040 | clburk4 | 8/9/2019 6:57:50 AM |
| DataCollection | No-POPPY Study Blood Collection Information Sheet.pdf | Blood collection sheet | 0.118 | cedu229 | 6/10/2019 7:17:50 AM |
| AdditionInfoConsiderations | Administrative supplement full proposal_Oct 2018.pdf | NIDA full proposal for additional sample analysis | 0.337 | cedu229 | 6/7/2019 7:19:34 AM |
| AdditionInfoConsiderations | Administrative supplement approval from NIDA_Oct 2018.pdf | NIDA approval for additional sample analysis | 0.110 | cedu229 | 6/7/2019 7:18:52 AM |
| AdditionInfoConsiderations | Memo to IRB regarding storing samples.pdf | Memo for the IRB regarding additional sample analysis | 0.503 | cedu229 | 6/7/2019 7:18:34 AM |
| Advertising | NACU_vs_Study_compared 11-29-18.pdf | | 0.037 | hlmurr2 | 11/29/2018 9:27:36 AM |
| StudyDrug | complete_Form O_morphine.pdf | Form O Morphine | 0.299 | cedu229 | 8/2/2018 12:56:15 PM |
| StudyDrug | complete_Form O_Clonidine.pdf | Form O Clonidine | 0.475 | cedu229 | 8/2/2018 12:56:02 PM |
| GrantContract | 3942049_Egrant.pdf | NIDA grant submission | 3.188 | cedu229 | 8/2/2018 12:52:32 PM |
| Advertising | Research Flyer NOPOPPYAPPROVED.pdf | Approved Flyer | 0.153 | cedu229 | 3/14/2018 3:09:26 PM |
| DataCollection | Order of Maternal Interviews.docx | Maternal Interview Measurement Items | 0.013 | cedu229 | 2/22/2018 12:12:55 PM |

## Protocol Changes

Protocol Number: 43976

Click link to sort Changed Date

HIPAA HIPAADeIdentificationCertForm changed by amwi284 on 12/16/2024 11:58:21 AM
N

Informed Consent ElectronicConsent changed by amwi284 on 12/16/2024 11:57:49 AM
N

Research Attributes ClinicalResearch changed by amwi284 on 12/16/2024 11:58:48 AM
Y

Research Attributes EpidemiologicBehavioralStudies changed by amwi284 on 12/16/2024 11:58:48 AM
N

Research Attributes MaterialOfHumanOrigin changed by amwi284 on 12/16/2024 11:58:48 AM
Y

Research Attributes OutcomesHealthServicesResearch changed by amwi284 on 12/16/2024 11:58:48 AM
N

Research Attributes PatientOrientedResearch changed by amwi284 on 12/16/2024 11:58:48 AM
Y

Research Sites MultisiteLeadInvestigator changed by amwi284 on 12/16/2024 11:58:27 AM
Y

## Study Personnel Changes:

| Status | PPIdentity | ProtocolID | PersonID | RoleInProtocol | IsContact | LastName | FirstName | Email | DeptCode | RoomBuilding | SpeedSort | PhoneNum | DeptDesc | AuthorizedConsent | ResponsibilityInProject | Degree | Rank | StatusFlag | IsRemoved | ModBy | ModDate | SFI | IsPI | RN | MiddleName |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inserted | 971880 | 101597 | 12595152 | SP | N | Mangino | Anthony | Anthony.Mangino@uky.edu | | | | | | N | Co-Investigator | PhD | | P | N | amwi284 | 12/16/2024 12:00:56 PM | N | | | |

No comments

Statistical Analysis Plan NCT03396588

Based on Consolidated Standards of Reporting Trials (CONSORT) standards, baseline demographic variables were summarized for morphine and clonidine treatment. Frequencies (%) are presented for categorical variables and either mean (SD) or median (min, max) for continuous variables. For outcome results, we present 95% confidence intervals (CIs).

A log-rank test was used to compare treatment arms regarding LOT and LOS. To use data from infants withdrawn from the study, the time of withdrawal was specified as the censoring time. Cox proportional hazards regression modeling was used in a follow-up analysis using treatment and selected risk factors associated with NOWS severity (birth weight, gestational age, gender, cesarean delivery, maternal psychiatric disorder, inborn status, MOUD, other opioid, and non-opioid substance use). Because smoking was highly prevalent and alcohol use was infrequent, they were not included in the model. In post hoc analyses, a negative binomial regression was used to model LOT for 115 infants, excluding those withdrawn from the study. Empirical SE estimates were employed to ensure valid inference.

Treatment arms were compared regarding the need for adjunct medication using frequencies (%) and x2 tests. Of 5 infants withdrawn, only 1 received adjunct medication; the other 4 were observed for <2 days. Utilizing data from all 120 infants, we assumed that the 4 infants did not require adjunct treatment. We also removed these 4 infants in a follow-up analysis. The remaining 116 infants were used to fit a logistic regression model, from which adjusted odds ratios were derived.

Wilcoxon rank tests were used to compare treatment groups regarding the timing between initial and final NNNS assessments and the NNNS scores (initial, final, and change). P values were adjusted using the false discovery rate method because of multiple comparisons across 13 summary scores. Intention-to-treat analyses used all available data based on treatment assignment. All tests were 2-sided, with a statistical significance of P <.05. Analyses were conducted in SAS v9.4 (SAS Institute Inc 2013. SAS/ACCESSVR 9.4 Interface to ADABAS: Reference. Cary, NC: SAS Institute Inc.).

Combined Consent and Authorization to Participate in a Research Study

**Non-Opiate treatment after prenatal Opiate exposure to Prevent Postnatal Injury to the Young Brain (No-POPPY)**

*When we say "you" in this form, we mean you or your child. "We" means the doctors and other staff.*

**WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?**
You are being invited to have your baby take part in a research study about drug withdrawal in newborns. Your baby may participate in this research because your baby may be withdrawing from the pain medicines or other drugs that you took while you were pregnant. If you volunteer for your baby to take part in this study, your child will be one of about 250 babies at the Kentucky Children's Hospital to participate.

**WHO IS DOING THE STUDY?**
The person in charge of this study at the Kentucky Children's Hospital is Dr. Henrietta S. Bada (Principal Investigator), Department of Pediatrics. Dr. Bada is a Neonatologist specializing in newborns withdrawing from medications or drugs they may have received before they were born. There may be other people on the research team assisting at different times during the study.

**WHAT IS THE PURPOSE OF THIS STUDY?**
Neonatal Abstinence Syndrome (NAS) is a group of withdrawal symptoms that can occur in babies when their mothers have taken pain medications or substances such as recreational or medical narcotics or drug treatments of methadone or subutex or suboxone during pregnancy; because medicines the mother takes while pregnant, the baby also takes. Babies usually develop symptoms of withdrawal within a few days of birth; your baby may experience withdrawal after delivery, and may need treatment. There are different ways to treat babies with NAS - about 50% of doctors use morphine, which is an opiate, to treat these babies, the rest use other drugs, such as clonidine or phenobarbital.

**The purpose of this study is to compare two different medicines to treat babies with withdrawal.** The treatment medicines in this study are morphine and clonidine. Morphine is a narcotic medicine, which is included in most pain killers. Clonidine is not a narcotic and has been used to treat other conditions as well as to help manage symptoms in babies with NAS. Both drugs are effective, but the purpose of this study is to see if one may be better than the other at reducing babies' symptoms and reducing how long they need to stay in the hospital. We will also be looking to see if there is a difference in how the babies grow and develop later in early childhood.

**ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?**
From the information we have about your baby, he or she qualifies to participate in the study. However, if your baby has had a seizure, or has been exposed to cocaine, your baby cannot participate. If your baby shows symptoms of withdrawal, he or she will still be treated for NAS with one of the standard medicines prescribed by your baby's doctor.

**WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?**
The research will be conducted at Kentucky Children's Hospital Neonatal Intensive Care Unit (NICU) and the NICU Graduate Clinic. The study will start when your baby needs treatment for withdrawal and continue until he or she is two years old. The treatment part of the study will end when your baby is discharged from the hospital. You and your baby will be asked to come to the NICU Graduate Clinic and have developmental assessments done when he or she is six months, one year and again at two years old.

**WHAT WILL YOU BE ASKED TO DO?**
Your baby will be monitored closely for symptoms of withdrawal, using a scoring method called Finnegan Scoring system. The baby's scores for withdrawal will differ according to the number of symptoms and the severity of symptoms. This system can be used for all babies with withdrawal whether they're in the study or not. If your baby's withdrawal scores increase or stay high, this means he or she needs medicine in order feel better, eat, sleep, grow, and be less fussy. If you agree for your baby to participate in this study, the pharmacy will randomize, or choose by chance (like a coin toss) whether to treat your baby with morphine or clonidine. There is a 50/50 chance of getting either drug. The medicine will be started immediately, but the nurses, doctors and you will not know which drug is being used – only the pharmacist. Both drugs will look alike and be given orally (by mouth). The medicine will be given every 3 or4 hours, depending on your baby's feeding schedule.

The Finnegan Scoring for withdrawal will be done routinely and based on your baby's scores; he or she may need an increase or decrease in the treatment dose. If your baby does not improve even after the drug is increased to the maximum, phenobarbital will be added. This is also a normal (standard) procedure in the NICU. If adding phenobarbital doesn't help your baby, another drug may be used at the doctor's choice.

The treatment medicine will be increased over time until your baby's scores start to improve. When your baby's Finnegan scores start improving (this may take days or weeks),this means that the amount of treatment medicine is helping to control your baby's withdrawal symptoms; then the amount of medicine will be slowly decreased(weaned) as long as your baby's symptoms remain controlled. If your baby scores go higher than normal again, his or her medicine will be increased till controlled and then slowly weaned again. Every baby is different - some babies may only need 10 to 14 days of treatment, while other babies may need up to 3 months.

Many babies have routine blood tests during the first 10 days of life. During these blood tests an extra amount of blood, about 1/8 of a teaspoon, will be drawn. These standard blood test may be done up to six times. The extra blood will be used to look at some DNA factors and to see how much of the treatment drug is in your baby's body. Your baby could receive extra blood draws for research purposes. These blood draws will be done randomly and close to the time your baby is ready to go home. These tests are to look at how quickly your baby's body has been processing the treatment medication (how much is still in their body).

Your baby will also have research assessments (called the NNNS), done in the hospital while still on drug treatment. The NNNS stands for NICU Network Neurobehavioral Scale and is used to see how your baby's behavior differs from other babies. The NNNS will be done twice – once in the beginning of withdrawal treatment, then when your baby is about a month old. The assessment involves observing or handling your baby to see how he or she acts and reacts (like self-calms, watching objects with eyes, etc.).

You will also be asked to return to the NICU Graduate Clinic when your baby is six months, one and two years of age. Your baby will have an Infant Behavior Questionnaire (6 mo), Bayley Assessments (6 mo, 1 and 2 years), and the Early Childhood Behavior Checklist (2 yr). These assessments are used to see how a baby's motor skills (physical abilities), cognitive skills (mental abilities) and behavior are developing. This takes about an hour and is done by the physical therapist. While you are at you baby's visit we would like to conduct a caretaker interview of continuing drug use, Parenting Stress Index, brief symptom inventory, and Beck Depression Inventory. We

understand many of our parents/caregivers need to drive 2 – 4 hour each way to attend a follow-up appointment in the NICU Grad Clinic, often both parents come and that is an entire day taken off from work. For study patients, there will be monetary assistance to off-set the cost of time and gas.

We may ask for additional contact information of friends or family members to ensure we are able to contact you throughout the length of the study. It is your choice to provide this contact information. The people you choose as contacts will not be given any private health information concerning you or your baby.

This table lists procedures that are standard of care procedures and procedures that are research procedures.

| Treatment | When | How long/often | Standard Care | Research |
|---|---|---|---|---|
| Finnegan Assessment | When withdrawal symptoms start | every 4-8 hrs till no symptoms | X | X |
| Treat with Morphine or Clonidine | When Finnegan scores are elevated and meet treatment protocol | Every 3 to 4 hours | X | X (because of randomization) |
| Phenobarbital | If 2nd drug is needed | Until withdrawal under control | X | |
| Blood Level | With other labs | Up to 4 times | X | X |
| Blood Level | Close to Discharge | Twice | | X |
| NNNS | Start of treatment and 1 month of age | Twice | | X |
| Infant Behavior Questionnaire | 6 month visit | Once | | X |
| Early Childhood Behavior Checklist CBCL | 2 year visit | Once | | X |
| Bayley Scores of Infant Development | 6 month, 1 and 2 years visit | 3 Times | X | X – travel/time assistance |
| Mother/Caregiver Interview and Questionnaires | Close to Discharge, 6 month and 2 year follow-up visit | 3 Times | | X |

**WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**

Your baby may have side effects from the medicines used to treat his or her withdrawal. Both of the medicines may cause constipation, vomiting, sweating, drowsiness or sleepiness, low blood pressure and even decreased breathing. None of these side effects happen very often in the NICU because the dose is usually not enough to cause the problems.

There are risks with drawing blood in babies, but since the doctors order other tests, the baby will be stuck anyway. The extra blood taken for this study will not increase the risks that already exist (pain, bleeding, infection, bruising, and soreness). Two additional blood draws will be done for research only. These blood draws carry the same possible discomforts and risks as if they were done as standard of care.

There is always a chance that any medical treatment can harm your baby, and the investigational treatment in this study is no different. In addition to the risks above, your baby may experience a previously unknown risk or side effect.

**WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?**

Your baby will be treated for symptoms of withdrawal, even if you do not agree to the study. One drug may be better than the other, but that won't be known until the study is over. One drug may require fewer days to

treat and may have fewer side effects. There is no guarantee, that your baby will get any benefit from taking part in this study.

**DO YOU HAVE TO TAKE PART IN THE STUDY?**
If you decide to allow your baby to participate in the study, it should be because you really want to volunteer his or her participation. Your baby will not lose any benefits or rights he or she would normally have if you choose not to volunteer your baby. You can stop at any time during the study and still keep the benefits and rights you had before volunteering.

**IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?**
If you do not want to take part in the study, your baby will be given standard care. At the Kentucky Children's Hospital, this is treatment with an opiate medication, and if additional medications are needed, phenobarbital is the first choice. Clonidine is also occasionally used rather than Phenobarbital.

**WHAT WILL IT COST YOU TO PARTICIPATE?**
You and/or your insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment your baby receives during this study that would normally be received for his or her condition. These are costs that are considered medically reasonable and necessary and will be part of the care your baby receives even if you do not allow him or her to take part in this study.

The Kentucky Children's Hospital is not allowed to bill your insurance company or Medicaid for the medical procedures done strictly for research. All research costs will be paid by a grant, and SHOULD not be billed to you. These research costs include the medicine he or she is given for withdrawal symptoms while he or she is a patient in the hospital, blood levels of the drug, special assessments (NNNS, Bayley's, IBQ,CBCL). If you have any questions regarding Medicaid coverage you should contact Medicaid at 1-800-635-2570.

**WHO WILL SEE THE INFORMATION THAT YOU GIVE?**
We will make every effort to keep private all research records that identify you and your baby to the extent allowed by law. Your baby's information will be combined with information from other babies in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. Your baby will not be personally identified in these written materials.

We will make every effort to prevent anyone who is not on the research team from knowing your baby's information, or what that information is. Your baby's information will be seen in the hospital electronic medical record files and the patient chart. The information required for the research study will be put in a password protected computer, located in the NICU Research Office (locked when not in use).

You should know that there are some circumstances in which we may have to show your baby's information to other people. Since your baby is a patient here at UK in the NICU, all the information used for research is the same as information used in the NICU. Officials of the Food and Drug Administration and the University of Kentucky may look at portions of records that identify your baby.

**CAN YOUR TAKING PART IN THE STUDY END EARLY?**
If you decide to allow your baby to take part in the study you still have the right to decide at any time that you no longer want to continue. You will not be treated differently if you decide to stop your baby from taking part in the study. In addition, the doctors conducting the study may need to withdraw your baby. This may occur if they find that the study is not benefiting your baby. If your baby is taken off study for any reason, the study drug will be stopped and your baby will have treatment as decided by your baby's doctor. Your baby will continue to

be closely monitored. If your baby is ready to go home, and is still receiving drug treatment, he or she will be taken off the study treatment. The doctors will decide whether to keep your baby on the same drug or change medicines. Since the study treatment will be over when your baby goes home, the medicine will no longer be paid for by the research grant. We ask that you continue with the follow-up behavior /development assessment visits at 6 months, 1 and 2 years.

**CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME?**
Your baby cannot participate in another study if enrolled in this study.

**WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?**
If you believe your baby is hurt or gets sick because of something that is due to the study, you should contact Dr. Henrietta Bada or the doctor on-call at the NICU clerk's desk - 859-323-5744 immediately. The clerk at the desk can have the doctor return your call. You can also ask your baby's nurse in the NICU to contact the doctor. The doctor will determine what type of treatment, if any, that is best for your baby at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because your baby gets hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if he or she is harmed by this study. The medical costs related to your baby's care and treatment because of research related harm will be your responsibility.

**WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?**
You will not receive any payment for allowing your baby to take part in the study. However, for study patients, there will be monetary assistance for time and to come to the follow-up visits, plus millage for travel costs.

| Visit | Amount |
|---|---|
| Discharge | $25.00 |
| 1 month ** | $50.00 |
| 6 months * | $50.00 |
| 1 year * | $75.00 |
| 2 year * | $100.00 |

*Round trip mileage reimbursement will also be included for each visit attended at the NICU Graduate Clinic.
** The 1 month assessment may take place while your baby is still in the hospital depending on how long their treatment lasts. If your baby has been discharged from the hospital before 1 month of age, we ask that you return to the NICU Graduate Clinic for this assessment and mileage will be included with this visit.

**WHAT IF YOU HAVE QUESTIONS, CONCERNS, or COMPLAINTS?**
Before you decide whether to accept this invitation to allow your baby to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact the investigator, Dr. Bada at 859-323-5744. If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky at 859-257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you.

**WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?**
If the researcher learns of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

**WHAT ELSE DO YOU NEED TO KNOW?**
The National Institutes of Health (NIH) has provided funding to help with this study. The study medicine is paid for by the NIH grant while your baby is in the hospital, but if he or she goes home still requiring treatment, you/your insurance will be responsible for that cost. The samples of blood that came from your baby might be used in studies that lead to new products for research, diagnosis or treatment. These products might have some commercial value. There are no plans to provide financial compensation to you should this occur.

**AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION**

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

**My and My baby's health information that may be used and released includes:**

- Date of Birth
- Gestational Age
- Birth weight
- Gender, Race, Ethnicity
- Date of NICU Discharge
- General clinical status/diagnoses information, and diagnoses dates
- Medications required during hospitalization
- Pregnancy, labor and delivery information
- Developmental Assessment at 6 months,1 and 2 years old

**My and My baby's health information will be used for:**

- Learning if there are better ways to treat babies with withdrawal symptoms using two different medicines.
- PHI is necessary to conduct the research, and meet legal, institutional and accreditation requirements

**The Researchers may use and share my baby's health information with:**

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- University of Kentucky representatives.
- UK Hospital
- Food and Drug Administration
- Investigational Drug Service (IDS) – to dispense the study drug
- National Institutes of Health (NIH)

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- **Current or future healthcare at the University of Kentucky**
- **Current or future payments to the University of Kentucky**
- **Ability to enroll in any health plans (if applicable)**
- **Eligibility for benefits (if applicable)**

**After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:**

- You will send a written letter to: Henrietta Bada, MD at 138 Leader Ave, Lexington, KY 40506 to inform her of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction.

The use and sharing of your information has no time limit.

**If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Mon-Fri at: (859) 323-1184.**

**You are the subject or are authorized to act on behalf of the subject. You have read this information, and you will receive a copy of this form after it is signed.**

_____ _____
Signature of research subject's legal representative Date

_____ _____
Printed name of research subject's legal representative Representative's relationship to research subject

*(*If, applicable)* Please explain Representative's relationship to subject and include a description of Representative's authority to act on behalf of subject:

_____

_____

_____ _____
Name of [authorized] person obtaining informed consent/HIPAA authorization Date

_____
Signature of Principal Investigator or Sub/Co-Investigator