NCT04298853

Optimal morphine dosing schedule for neonatal abstinence syndrome

Version: June 16, 2021

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[Date]

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Abbreviations

AE	Adverse Event
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
NAS	Neonatal Abstinence Syndrome
PI	Principal Investigator
SAE	Serious Adverse Event

1.0 Background & Rationale

Neonatal abstinence syndrome (NAS) is a pattern of withdrawal symptoms seen in newborn infants who are exposed to opioids in utero. The incidence of this condition has increased drastically over the last two decades as a result of the ongoing nationwide opioid epidemic.[1-3] In 2015, the NICU at Indiana University Health Methodist Hospital implemented a guideline for the management of NAS. This guideline includes the modified Finnegan scoring tool to assess severity of withdrawal symptoms and guide interventions, particularly when it is appropriate to initiate pharmacologic treatment. This guideline was successful in reducing the mean length of stay for infants treated for NAS from 27.7 days to 19.7 days. However, the average length of stay has remained stable since then and concerns have been raised that we may be treating infants too aggressively based on this guideline. In 2018, a total of 154 infants (≥ 35 weeks gestation) with intrauterine opioid exposure were born at IU Health Methodist Hospital. Of these infants, 43% (66 infants) required treatment with morphine with an average length of stay of 21.5 days.

Currently there is no uniformly accepted treatment strategy for NAS and both the choice of primary medication and criteria for treatment vary widely.[4,5] Morphine is by far the most commonly used medication for NAS treatment, followed by methadone.[6,7] Buprenorphine is also gaining interest and appears to be a viable option for treatment of NAS in terms of safety and feasibility of dosing.[8] Based on a small number of randomized trials and retrospective cohort studies, it appears to be superior in terms of length of treatment in comparison to methadone and morphine.[8-10] However, there is still a need for larger scale studies. In neonates, buprenorphine is administered sublingually in a solution of 30% ethanol and is not as readily available in this form. The question of which medication is optimal to treat NAS is highly debated. Many studies seeking to answer this question have been published, but due to variability of multiple factors and overall low quality of evidence, it is difficult to come to a single conclusion regarding appropriate medication choice and dosing schedule.[10] We have chosen to use morphine as it is readily available, has been used widely in newborns, and has a shorter half-life which makes it easier to titrate dosing quickly for symptom management.

The starting dose of morphine and protocols for adjusting the dose are variable as well. In general, most institutions use a starting dose of 0.04 – 0.05 mg/kg of morphine given every 3-4 hours. Our current practice is to use 0.05 mg/kg every 3 hours and to increase the dose as needed based on response, measured by the modified Finnegan score. Once an infant is stable for 48 hours on a particular dose, the weaning phase is initiated. A stable condition is defined as a modified Finnegan score less than 9, eating well, gaining weight and sleeping. However, Grossman et al had success in decreasing the length of stay for infants with NAS using intermittent/as needed morphine dosing in combination with a novel approach to scoring.[11] In this model, infants are monitored with a scoring system and a dose of morphine is only given if the infant meets specified criteria for treatment, with a minimum interval of 3 hours between

doses. While this is promising, there have been no studies thus far comparing as-needed morphine dosing to the current standard approach of scheduled dosing with gradual weaning of the dose. This is an important piece of information as many centers are seeking to adopt this method without the supporting evidence of a randomized trial.

2.0 Objective(s)

2.1 Primary Objective: To evaluate the feasibility of conducting a randomized controlled trial by examining enrollment.

2.2 Secondary Objective: To evaluate the feasibility of conducting a randomized trial by identifying any concerns related to the practicality of the study protocol.

2.3 Tertiary Objective: To provide an estimate of means and standard deviations necessary to conduct a definitive RCT.

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measure: Enrollment rate, drop out rate, number of patients switched to standard arm

3.2 Secondary Outcome Measure: Length of hospital stay from birth to discharge,

3.3 Total cumulative morphine exposure (per kilogram of body weight), peak morphine dose, and length of morphine treatment (in days)

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Neonates ≥ 35 weeks gestation with intrauterine opioid exposure
- Severe NAS (modified Finnegan score ≥9) requiring NICU admission

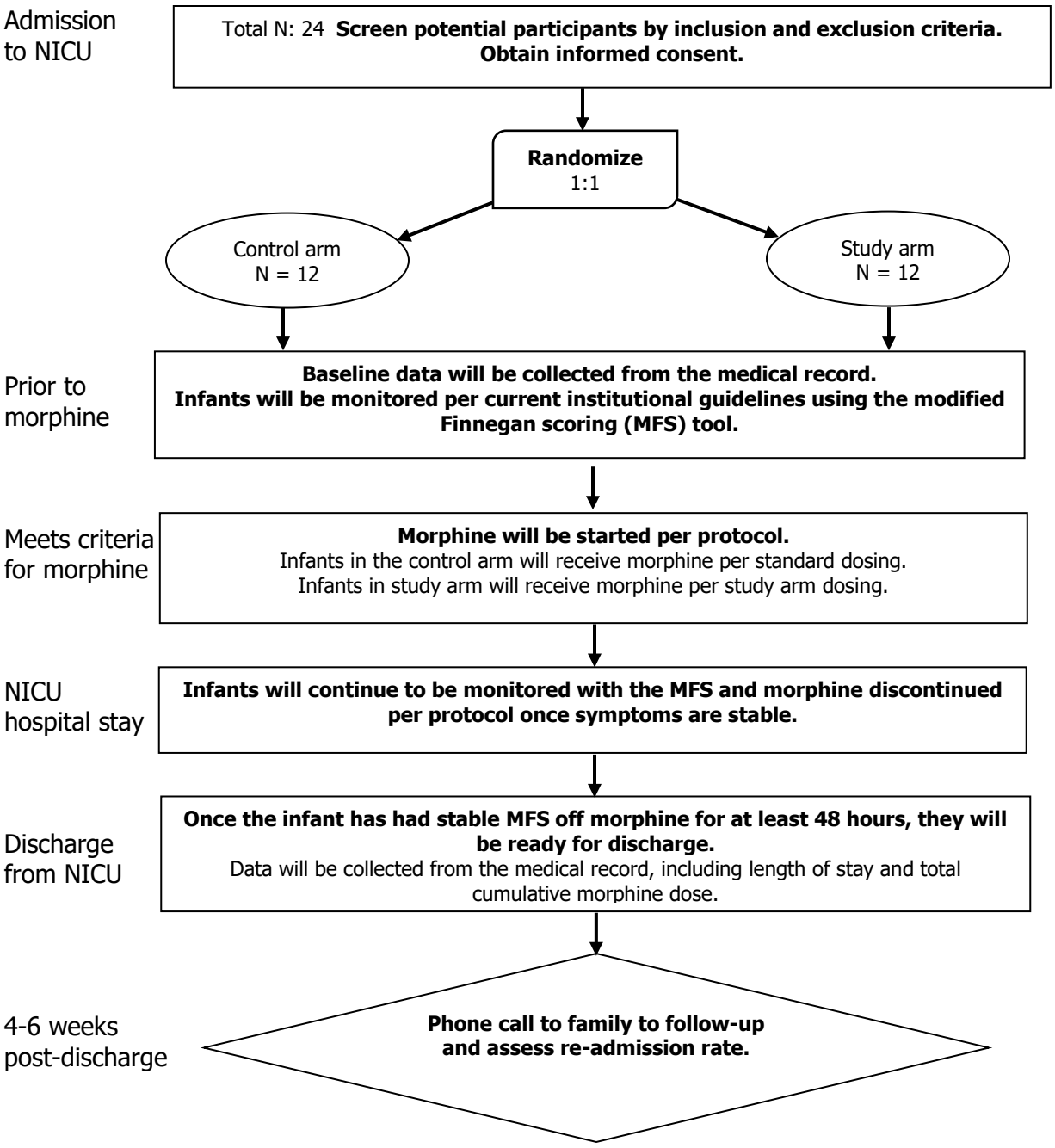
4.2 Exclusion Criteria

- Infants with significant co-morbidities requiring analgesia or sedation due to clinical condition
- Infants with ongoing need for respiratory support
- Infants with suspected genetic abnormalities or significant congenital anomalies that would interfere with accurate modified Finnegan scoring or response to oral morphine
- Mother and baby pairs in which the mother is under the age of 18 years old

5.0 Study Design

This will be a pragmatic pilot randomized controlled trial comparing scheduled versus intermittent morphine dosing for severe neonatal abstinence syndrome, performed in the Riley Hospital for Children Neonatal Intensive Care Unit (NICU) at IU Health Methodist Hospital. In 2018, 154 babies admitted to IU Health Methodist were exposed to opioids in utero. Dr. Anna Thomas has clinically treated and conducted research with this population since 2015. We hypothesize that treating NAS symptoms on an as-needed basis will result in decreased use of morphine and decreased length of stay. Severity of NAS will be defined by the modified Finnegan scoring tool, which is already in use.[12] This tool is administered by the bedside nurse

every 3-4 hours and uses graduated scoring of 21 items which are then added together to give the modified Finnegan score.
The current guideline for pharmacologic treatment of neonatal abstinence syndrome uses the modified Finnegan score to determine the severity of symptoms. Modified Finnegan scoring should be performed every 3 hours after a feeding. If an infant reaches the threshold score for treatment ($\geqq$ 9), morphine is initiated at 0.05 mg/kg/dose orally every 3 hours. If the modified Finnegan score continues to be elevated, the dose is escalated per a protocol until the modified Finnegan score is in an acceptable range. Once the infant's modified Finnegan score has been stable for at least 48 hours on a particular morphine dose, the weaning phase begins. Morphine is weaned by 10% of the peak dose every 24 hours as tolerated based on symptoms. When the dose has been weaned to < 0.02 mg/kg/dose, it may be discontinued. In order to be discharged home from the hospital, the infant needs to remain stable off of morphine for at least 48 hours. The study group will also be assessed using the modified Finnegan scoring tool. These infants will receive morphine at the same starting dose of 0.05 mg/kg/dose but on an as-needed basis as often as every 3 hours if the modified Finnegan score reaches the threshold for treatment. Our goal is to enroll 24 participants with 12 patients on each arm. A success rate would be a retention of 80% (approximately 20 participants).



6.0 Enrollment/Randomization

Patients will be assessed for eligibility at the time of birth based on known intrauterine opioid exposure. The parents will not be approached for participation in the study unless the infant is admitted to the NICU with severe NAS symptoms. If eligible, the mother will be approached for informed consent upon admission to the NICU or, if already admitted to the NICU, upon recognition that the infant has severe symptoms that may need morphine. Once consent has been obtained, the infant will be randomized via paper process that has been designed by a biostatistician in block sizes of 4-6 patients with a 1:1 ratio. Randomization can occur after the first dose of morphine as the second dose of morphine is considered a study procedure.

7.0 Study Procedures

Newborns will be screened for enrollment if they are exposed to opioids in utero. We will not approach the parents of infants with opioid withdrawal if they are stable and remain in the well newborn nursery. Once the newborn is enrolled and randomized prior to the second dose of morphine they will continue to be monitored per standard care with the modified Finnegan score. Information will be collected from the mother's medical chart, including her age, medical problems, Hepatitis C status, labor and delivery complications, prior history of drug use, current medications, prenatal screening labs, and urine toxicology results. Information will also be collected from the newborn's chart, including gestational age at birth, mode of delivery, Apgar scores, birth weight, modified Finnegan scores, length of time in the newborn nursery prior to NICU admission, nutrition (breastfeeding vs formula), urine, meconium, and umbilical cord toxicology screens.

All infants will receive optimal non-pharmacologic interventions per standard care, such as parental rooming-in when possible, breastfeeding when possible, quiet and dimly-lit environment with low stimulation, close contact with caregiver for soothing, pacifier, and on-demand feedings.

Each group will be monitored with the use of the modified Finnegan score to quantify the severity of NAS, per the current standard care. **It is performed by the bedside nurse every 3-4 hours following a feeding**. Due to the pragmatic nature of this pilot trial, FINN scores obtained outside this window will not be a deviation. Bedside nursing is trained in the modified Finnegan scoring process. If a patient meets the threshold for morphine (modified Finnegan score $\geqq 9$, or a score of $\geqq 12$), a second nurse should immediately perform a separate score to confirm. The threshold for initial dose of morphine will be the same for both the standard care control and the study group. All infants with intrauterine opioid exposure will remain inpatient for observation for a minimum of 5 days before discharge, per standard care. The details of treatment for each group are outlined below.

Standard Care (Control) Group

1. Initiation of morphine and stabilization
    a. Non-pharmacologic care (infant soothing techniques) should be optimized prior to initiating morphine or increasing the dose. If the clinical team feels non-pharmacologic care has not been optimized, it is appropriate to do so and re-evaluate the next modified Finnegan score before initiating or increasing morphine.
    b. Treatment should be initiated if an infant has **two** consecutive modified Finnegan scores ≥ 9 or one score ≥ 12.
        i. Initial dose: morphine 0.05 mg/kg/dose every 3 hours.
    c. Modified Finnegan scoring will continue every 3 hours.
        i. If the infant's modified Finnegan score remains ≥ 12, a rescue dose of double the previous dose should be given. For instance, if an infant is given 0.05 mg/kg/dose and the next modified Finnegan score is ≥ 12, a rescue dose of 0.1 mg/kg/dose should be given x1.
        ii. If the modified Finnegan score is < 12 after the rescue dose is given, that dose should be given as the maintenance dose every 3 hours.

iii. If the modified Finnegan score remains > 8 but < 12, escalate the morphine dose by 0.03 mg/kg/dose every 3 hours until the scores are ≤ 8.

iv. Before increasing the dose, ensure that there has been sufficient time to observe the patient's response to the previous dose given. For example, if an infant receives a morphine dose at the time of a feeding, the Finnegan score is then assigned 1 hour after the feeding. This is not sufficient time to reflect the response to the most recent morphine dose. There should be a full period of observation (at least 2 hours) after a dose before a decision is made to escalate the dose.

d. Once the modified Finnegan scores are consistently ≤ 8, continue the maintenance dose for 48 hours before beginning the weaning phase.
e. If the morphine dose exceeds 0.3 mg/kg/dose, consider adding phenobarbital as an adjunctive medication.
   i. Loading dose: phenobarbital 10 mg/kg/dose q12 hours x2 doses
   ii. Maintenance: phenobarbital 5 mg/kg/dose q24 hours

2. Weaning
   a. Once the infant has been stable for 48 hours, begin weaning the dose of morphine by 10% of the original maintenance dose (the dose on which the infant has been stable) every 24 hours. For example, if the maintenance dose is 0.05 mg/kg/dose, each wean should decrease by 10% of that dose = 0.005 mg/kg/dose.
      i. Maintain the dosing interval of every 3 hours throughout the entire weaning process.
   b. If the infant has two consecutive modified Finnegan scores ≥ 9, increase back to the previous dose at which the infant was stable.
      i. If modified Finnegan scores continue to be > 8 after going back to the previous dose, continue to increase the dose in a stepwise fashion. Consider weight-adjusting the dose if appropriate.
      ii. Remember to optimize non-pharmacologic measures and rule out other causes of agitation before increasing the dose.
   c. Once the infant is stable again for 48 hours, resume weaning by 10% of the original maintenance dose.
   d. Once a single dose is < 0.02 mg/kg, discontinue morphine.
   e. If the infant is receiving phenobarbital, discontinue at second to last step of morphine wean.
   f. Infants should be monitored for a minimum of 48 hours after discontinuing morphine prior to discharge.
   g. **If the infant qualifies for treatment based on modified Finnegan scoring AFTER discontinuation of morphine, restart morphine at the previous dose at which the infant was stable (the ending dose of the weaning schedule).**
      i. Once infant is stable for 48 hours, consider weaning an additional step prior to discontinuing morphine.
      ii. If the infant meets criteria for a rescue dose, give a one-time dose of double the previous dose at which infant was stable.

i. For example, if the previous dose at which the infant was stable was 0.07 mg, give 0.14 mg x1 and resume the maintenance dose at 0.07 mg. Do not use 0.14 mg as the new maintenance dose unless infant requires a repeat rescue dose.

Study Group

1. Non-pharmacologic care (infant soothing techniques) should be optimized prior to giving a morphine dose. If the clinical team feels non-pharmacologic care has not been optimized, it is appropriate to do so and re-evaluate the next Finnegan score before giving morphine.
2. If the modified Finnegan score is ≥9 for **two** consecutive scores or ≥ 12 for one score, the infant will be given a one time dose of 0.05 mg/kg of morphine orally.
3. If any subsequent modified Finnegan score is ≥ 9, the infant may receive a repeat dose of morphine 0.05 mg/kg. Before repeating a dose, there should be an adequate period of observation after the prior dose was given (at least 2 hours) for the Finnegan score to reflect the response to a dose.
    a. If an infant has received 3 consecutive doses of 0.05 mg/kg/dose every 3 hours and continues to qualify for a 4th dose consecutively, that dose will be increased to 0.075 mg/kg/dose
    b. The infant will then receive 0.075 mg/kg dose when indicated.
    c. The morphine dose may be escalated to 0.1 mg/kg if the infant receives 3 consecutive doses of 0.075 mg/kg and again qualifies for a 4th consecutive dose
    d. If it has been more than 24 hours since the previous dose of morphine and the infant again qualifies for a dose, it will be decreased back to the lower dose
4. If an infant receives all 8 possible doses of morphine within a 24-hour period (i.e. the infant receives morphine every 3 hours for 24 hours consecutively), the infant will be removed from the study protocol and placed on morphine per the standard guideline
5. An infant will be eligible for potential discharge once they have been stable for 48 hours without receiving a dose of morphine.

8.0 Study Calendar

Timeline	**Birth**	**Admission to NICU**	**Treatment**	**Discharge**	**Follow-up**
Study Procedures	Screening for potential eligibility based on opioid exposure	Determine eligibility and approach for enrollment	Follow treatment course	Final data collection on outcomes	Phone call/chart review) at 4-8 weeks of age to assess for re-admission
		Collect baseline maternal and newborn data	Monitor for protocol deviations, issues, AEs, SAEs	Confirm contact information for follow-up phone call	
		Randomize	Continue data collection		

9.0 Reportable Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject in the investigation. AEs must be assessed for expectedness, severity, attribution (relatedness to the study intervention), and seriousness by the investigator, or another qualified study team member as characterized below. AEs deemed related to the intervention must be reported as serious adverse events (SAEs) if they become serious (become life-threatening, result in death, or prolong hospitalization). Recording of such adverse events will start at the time of the study consent and will stop upon discharge from the hospital.

The following criteria will be used to define relatedness:
Definite: The AE is clearly related to the study intervention
Probable: The AE is likely related to the study intervention
Possible: The AE may be related to the study intervention
Unrelated: The AE is clearly not related to the study intervention
The severity of AEs will be described as:
Mild: asymptomatic or mild symptoms, no intervention indicated
Moderate: clinically significant requiring minimal noninvasive intervention
Severe: severe or medically significant but not immediately life-threatening, need for intensive, emergent, or invasive intervention
Life-threatening: life-threatening physiological consequences, need for intensive or emergent invasive intervention

Newborns with NAS are at risk of several complications related to their withdrawal symptoms. They may experience excessive weight loss in the first 1-2 weeks of life (>10% of their birth weight), they may have oromotor dysfunction and require supplement gavage feedings to support growth, and in rare cases, they can have seizures. Adverse events will be monitored monthly by the study team and collected in REDCap. Infants who receive morphine are at risk of over-sedation and decreased level of consciousness, as well as respiratory depression that can result in apnea. While this risk is mitigated by the fact that infants with NAS are opioid-tolerant, it remains a risk especially when escalating the dose. Per standard care, all infants receiving morphine remain on cardiopulmonary monitoring throughout their treatment.

Adverse Event monitoring will include:
1. Depressed level of consciousness
    - Grade 1: Decreased level of alertness
    - Grade 2: Sedation; slow response to stimuli; sleeping longer than expected or needing to be aroused at feeding times
    - Grade 3: Difficult to arouse
    - Grade 4: Life-threatening consequences; coma; urgent intervention indicated
    - Grade 5: Death
2. Other events classified as serious and unexpected
3. Other events resulting in death or classified as Serious or Related (to study procedures)

A depressed level of consciousness grades 1-3 will be considered an AE, while grade 4 will be considered a SAE. All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. All deaths and SAEs that are at least possibly related and all unexpected SAEs will be

reported to the investigator within 24 hours of the study team becoming aware. An initial SAE form must be as complete as possible, including details of the current serious adverse event, including an investigator assessment of the causal relationship between the event and study procedures. Information not available at the time of the initial report must be documented on a follow-up SAE form. All unexpected SAEs will be reported to the IRB within 5 working days. The study team will begin tracking AEs and SAEs at the time of consent and will conclude tracking after the follow-up phone call has been made when the infant is 4-8 weeks of age.

We will not report deviations as clinical care is being followed. This is a pragmatic pilot trial that is not intended to alter the standard of care treatment. It is ideal that the morphine is dosed every 3 hours/FINN scores obtained for those on the standard arm. However, there will be times this does not occur, and it will not be considered a protocol deviation.

10.0 Data Safety Monitoring

Given that this will be a small pragmatic pilot study, data safety monitoring will be done by the study team. The neonatal research nurses/coordinator will monitor data quality, subject recruitment, accrual, retention, outcome and adverse event data, and procedures designed to protect the privacy of subjects on a monthly basis. Any AE or SAE will be immediately discussed as described above. The study team, consisting of neonatal research nurses, coordinators, and the PI, will meet every 6 months to review the above factors as well as the results of any related studies that may impact subject safety.

11.0 Study Withdrawal/Discontinuation

Infants may be withdrawn from the study at any time at the request of the parent(s). If withdrawn from the study, they will receive standard treatment for neonatal abstinence syndrome, consistent with the control group. Infants may also be withdrawn from the study if there is a change in clinical status rendering it necessary to deviate from the study protocol per physician discretion.

12.0 Statistical Considerations

Based on previous data a sample size of 108 per group would be necessary to have 80% power to detect a 5-day reduction in length of stay; this is not feasible for a single site trial. In order to better design a larger RCT, a pilot study will be conducted.
A sample size of 12 per group has been suggested as appropriate for pilot studies to evaluate feasibility and to estimate means and standard deviations.[13] All calculations assume a two-sided two-sample t-test conducted at a 5% significance level. This pilot data will be necessary to design a larger scale randomized trial.

13.0 Statistical Data Management

Data management and interpretation

Data will be collected using prepared forms, then entered and managed using REDCap electronic capture tools hosted and managed by IUPUI Biostatistics. The REDCap platform is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to

common statistical packages and 4) procedures for importing data from external sources. Only IRB approved research team members will have access to the REDCap data platform. Each team's members will be granted access to the REDCap data system through a secure login. In the REDCap data platform, primary data and data backups are secured at separate Indiana University Data centers. Operating system security includes: secure logins, data encryption at rest, remote system logging and configuration and change management. Data backups are encrypted both in flight and at rest. Copies of data are replicated to the remote data center every 15 minutes. There are 100+ point-in-time copies of data available at any time. Disaster recovery has been tested and confirmed.

Performance Monitoring: Standard reports can be generated from the study database by the research office. These will include monthly reports that provide the number of infants enrolled, missing data, adherence to study protocols, and a variety of performance measures, including adverse events.

14.0 Privacy/Confidentiality Issues

Security measures to protect subject identities include the use of coded files to unlink research records from names and other identifiers, locked storage areas, and password-protected computer files. Subjects' names are linked to their IDs as noted above. Access to computer systems housing sensitive information is strictly regulated. Credentials permitting access to these systems are granted only to essential investigators and research personnel. All systems are secured from external attack through a combination of hardware and software firewalls and are updated with necessary security patches as they become available. Related hardware and back-up storage media are maintained in a secure environment to which only essential personnel have physical access. All consent and research procedures will be compliant with Subpart B of the Code of Federal Regulations Title 45, Part 46 - Protection of Human Subjects with Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (66 FR 56778, Nov. 13, 2001).

15.0 Follow-up and Record Retention

The duration of the study will from be from enrollment through 4-8 weeks of age. The majority of the data collection and monitoring will be done during the initial hospital stay. Once the infant is discharged from the NICU, we plan to contact the parent via phone for follow-up to determine if the infant has required readmission to the hospital for any issues potentially related to neonatal abstinence syndrome in the first month of life. If the baby stays in the IU Hospital system after birth, the study team will look for recent appointments that may contain the follow up information.

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Appendix 1.0

Modified Finnegan Scoring Tool.
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NEONATAL ABSTINENCE SCORING SYSTEM

SYSTEM	SIGNS AND SYMPTOMS	SCORE	AM					PM						COMMENTS
CENTRAL NERVOUS SYSTEM DISTURBANCES	Continuous High Pitched (or other) Cry	2												Daily Weight:
	Continuous High Pitched (or other) Cry	3												
	Sleeps <1 Hour After Feeding	3												
	Sleeps <2 Hours After Feeding	2												
	Sleeps <3 Hours After Feeding	1												
	Hyperactive Moro Reflex	2												
	Markedly Hyperactive Moro Reflex	3												
	Mild Tremors Disturbed	1												
	Moderate-Severe Tremors Disturbed	2												
	Mild Tremors Undisturbed	3												
	Moderate-Severe Tremors Undisturbed	4												
	Increased Muscle Tone	2												
	Excoriation (Specific Area)	1												
	Myoclonic Jerks	3												
	Generalized Convulsions	5												
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES	Sweating	1												
	Fever 100.4°-101°F (38°-38.3°C)	1												
	Fever > 101°F (38.3°C)	2												
	Frequent Yawning (>3-4 times/interval)	1												
	Mottling	1												
	Nasal Stuffiness	1												
	Sneezing (>3-4 times/interval)	1												
	Nasal Flaring	2												
	Respiratory Rate >60/min	1												
	Respiratory Rate > 60/min with Retractions	2												
GASTRO-INTESTIONAL DISTURBANCES	Excessive Sucking	1												
	Poor Feeding	2												
	Regurgitation	2												
	Projectile Vomiting	3												
	Loose Stools	2												
	Watery Stools	3												
	TOTAL SCORE													
	INITIALS OF SCORER													