Protocol Title: Methadone Demonstration Project

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

The Problem:

Infants who are born to mothers taking or abusing opiates frequently suffer from neonatal abstinence syndrome (NAS) after birth. They often have withdrawal symptoms which can be life-threatening if untreated. The American Academy of Pediatrics (AAP) recommends non-pharmacologic treatment as first-line therapy, followed by opioid replacement for severe cases. The pharmacologic treatment usually takes place within the hospital setting. Such approach often incurs prolonged hospitalization and significant financial burden. It also creates barriers to adequate maternal/infant bonding with potential deleterious consequences for the infant's long term emotional and societal outcomes.

The Research Hypothesis: Among Neonatal Intensive Care Unit (NICU) infants diagnosed with NAS and requiring pharmacological treatment, those who are treated with methadone will have a shorter Length of Stay (LOS) of less than 15 days as compared to the average length LOS of 25 days of NAS infants admitted in recent years at Johns Hopkins All Children's Hospital (JHACH) NICU.

The Importance of the Research:

Infants suffering from NAS are historically cared for in the hospital setting and are not discharged home until all narcotic medications have been weaned off. Such prolonged hospital stay invariably equates to prolonged separation of mother and baby. Consequently, infants suffer from the absence of a care giver who could provide constant comforting techniques which are the mainstay of treatment of infants with NAS. This in turn leads to further prolongation of the hospital stay and impaired mother-infant bonding.

This demonstration project has the potential to improve short and long term outcome of infants suffering from NAS while decreasing the cost of their care. It aims at doing so by 1) reaching out to qualifying mothers prior to delivery; 2) empowering those mothers during their infant hospital stay by further educating them on NAS and means of comforting and easing their infant's withdrawal symptoms; 3) discharging infants home while still on narcotic treatment under very close medical supervision until complete weaning is achieved; 4) ensuring a safe home environment and healthy maternal involvement throughout withdrawal and for a year after cessation of medical treatment.

2. **Objectives**

Primary Objective: Compare the LOS of NICU infants with NAS treated with methadone with historical data and a comparison group of NICU NAS infants treated with a different narcotic agent.

Secondary Objectives:

1) Compare maternal bonding between methadone treated infants and those treated with a different narcotic,
2) Assess if methadone treatment leads to decreased maternal depressive symptomatology as compared to treatment with other narcotics;
3) Study whether methadone treatments leads to safer transition to home with no readmissions to the hospital within 30 days for NAS-related reasons;
4) Compare proportions of children who gain weight (greater than 15% above birth weight) at 30 days of age between methadone treated and non-treated infants;
5) Compare the incidence of providing breast milk (> 50% of nutritional needs) at 30 days of age between methadone treated and non-treated infants;
6) Assess the age appropriate infant development at 4, 8 and 12 months of age among the methadone treatment group;
7) Determine the response percentage of mothers who are screened as eligible by PAR officials and who agree to participate in the demonstration project;
8) Assess the drop out percentage of mothers who agree to participate but do not follow through with home discharge for continued care;
9) Quantitate the proportion of mothers who feel comfortable with home care of their infant at discharge;
10) Monitor the readiness of mothers to assess infant on 3 to 4 hours intervals while at home;
11) Determine the compliance rate with the Johns Hopkins All Children's Hospital (JHACH) pediatrician visits.

The authors hope to add a long-term follow-up study that will involve the evaluation of the infants development at set points utilizing standardized testing (18, 36, 48 and 60 months) with a goal of putting interventions in place if development is lagging, and with the ultimate goal of improving school readiness for this population. A separate application for this follow-up study will be filed if funding is secured.

3. **Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Pre-Clinical and Clinical Data: Pre-clinical data is not applicable for this project

The scope of the problem:

Illicit drug use among pregnant women is a tremendous problem. The Mental Health Services Administration Survey reports 4.4-5.1% of pregnant women used illicit drugs in the United States in 2010 (*SAMHSA, 2011*). The number of pregnant women using opioids during pregnancy increased five-fold between 2003 and 2013 (*Patrick, 2012*), with 1.1 % of pregnant women reported to use opioids in 2011 (*SAMHSA, 2013*). Between 55% and 95% of infants exposed to maternal opioids *in-utero* develop the withdrawal symptoms of NAS after their opiate intake is suddenly cut-off at the time of placental separation (*Hudak, 2012*) with a 60 to 80% risk of NAS requiring pharmacologic treatment. The incidence of NAS varies by geographic distribution, and the hospital length of stay to treat it varies among different institutions. The frequency of NICU admissions for the treatment of NAS in 2013 was reported as 27 cases per 1000, with a median length of stay of 19 days (*Tolia, 2015*).

NAS is manifested by central nervous system irritability (high pitch and inconsolable crying, irritability and sleep disturbances), autonomic nervous system over-reactivity (sweating, yawning, sneezing), gastrointestinal manifestations (poor feeding, emesis and loose stools) and respiratory distress (tachypnea and nasal congestion) (*Finnegan 1975; Finnegan, 1976; Kaltenbach, 1986; Desmond 1975*). The standard of care is to treat these infants with a slow taper of opioid but to date there is no established gold standard for that taper (*Cochrane, 2010*). The lack of high-quality research in the treatment of NAS has led to wide variations in medications and protocols (*Patrick, 2014; O'Grady, 2009; Sarkar, 2006)*) and data on changes in the utilization of NICU resources in the treatment of affected infants are lacking (*Tolia, 2015*).

For the time frame July 1, 2013 through September 30, 2014, 300 infants with NAS have been cared for at the Johns Hopkins All Children's Hospital (JHACH) NICU with an average length of stay of 30 days. The average length of stay has recently decreased to 22-25 days with implementation of strict management guidelines and protocols. Accounting for an average daily cost of $2062.50, the burden translates into medical costs averaging $48,468.75 per infant. With the proposed model involving methadone treatment, we anticipate at most 14 days of care in the NICU at a cost of $28,875.00, followed by 10 days of home care at an anticipated cost of $190/day for a total cost of $30,775. This is an anticipated reduction in cost of $17,693.75 per patient.

The prolonged stay has other social and medical impacts – including limitation in parental interaction and bonding, exposure to nosocomial infections, and taking up valuable resources both in terms of personnel and equipment. Once discharged home, these infants are often exposed to inconsistent caregiving, family instability, out of home placements, chronic stress, abuse, neglect and poverty – all of which affect their health and development, thus incurring even greater societal costs. To date, there are no published data on the in-home pharmacologic treatment of these infants.

A number of institutions across the USA including our affiliate hospital, Sarasota Memorial Hospital, have historically allowed for infants with NAS to be discharged home on methadone. However, concerns over mothers providing the medication themselves have led to stopping the practice at Sarasota. At-home administration is still offered to select patients at some non-affiliate Tampa area institutions, whereby a prescription for a 2-week supply is given and parents are trained and cleared for its administration.

To date, there are no published data on the in-home pharmacologic treatment of these infants.

Non-Pharmacological management in Neonatal Abstinence Syndrome Treatment:

The American Academy of Pediatrics advocates for the initial treatment of infants with NAS to be non-pharmacologic in nature (*AAP Committee on Drugs, 1998*). It is to be directed at 1) minimizing environmental stimuli (like light and noise), 2) lessening the infants' auto-stimulation with careful swaddling and optimal positioning, 3) lessening hunger with small frequent meals and 4) providing timely comforting techniques with quick response to the infants' needs and signaling. The latter could be provided best through maternal education, involvement and empowerment. Mothers who are on monotherapy in a rehabilitation program are highly encouraged to breastfeed their infant (Gartner, 2005; Jansson, 2009).

The quality of the relationship between mother and her infant directly influences the structure of the child's affective ties and overall organization of responses to environment (*Ainsworth, 1969; Ainsworth, 1978; Bowlby, 1969/1982*). Attachment is an ongoing process, initiated during pregnancy and developed over time. This mother-infant bond sets the stage for understanding and identifying the infant's needs and reciprocal parental response to those needs (*Bowlby, 1980*). Maternal emotional unavailability has potentially serious effects on the long-term mother-child relationship, and on the child's development.

Infants suffering from NAS have poor regulatory mechanisms. Those infants who require medical treatment for their symptomatology have more dysregulated behavior, greater difficulty modulating arousal and yielding appropriately organized responses, and are more irritable (*Velez, 2009*). Such "difficult" infants are invariably hard to care for and difficult to console and they provide an emotional challenge to their caretakers. This challenge becomes even more significant when the caretaker is the mother who is suffering from addiction and is already emotionally compromised by feelings of depression, anxiety, guilt or insecurity.

Tools for assessing the maternal-infant bonding:

Different tools have been reported in the literature assessing the maternal-infant bonding.

The Postpartum Bonding Questionnaire (PBQ) aims to identify problems in the mother-baby relationship based on four components: 1) weakened bonding, 2) rejection and pathological rage, 3) anxiety about the baby/anxiety about caring for the baby, 4) imminent abuse/risk of abuse. The PBQ is a 25-item questionnaire, rated on a 6-point Likert scale. Reliability coefficients ranged from α=0.74 to α=0.95 (*Brockington*, 2006)

The Edinburgh Postnatal Depression Scale (EPDS) was developed for screening postpartum women in outpatient, home visiting settings, or at the 6–8 week postpartum examination. It has been utilized among numerous populations including U.S. women and Spanish speaking women internationally. The EPDS consists of 10 questions. The test can usually be completed in less than 5 minutes. Responses are scored 0, 1, 2, or 3 according to increased severity of the symptom. The split-half reliability of the scale was found to be 0.88, and the standardized Cronbach's alpha-coefficient 0.87. (*Cox, 1987*).

Opioid Replacement in Neonatal Abstinence Syndrome Treatment:

The goal of an effective tapering regimen is to minimize infant discomfort and, as much as possible, to restore counter adaptive cellular mechanisms to achieve homeostasis. Opioid replacement and tapering is the most widely used and agreed upon starting point of therapy (*Kraft, 2016*). However, the best choices of opiate and titration regimen are yet to be determined. To date, fewer than 10 prospective randomized controlled trials (RCT) in infants that meet inclusion criteria for a Cochrane analysis have been published. The opioid preparations that have been trialed in these studies include methadone, paregoric, morphine, tincture of opium and buprenorphine. The statement from the American Academy of Pediatrics states that given the lack of adequate comparative studies, no optimal pharmacologic regimen can be recommended. The goal of any regimen however is to achieve the desired therapeutic effect by using the fewest drugs at the lowest doses and for the shortest durations possible. Morphine or Methadone are suggested as first line of management (*Hudak*, 2012).

Methadone as a first line treatment for opiate withdrawal in newborn Infants:

The AAP and multiple reviews recommend opioid replacement as first-line pharmacotherapy treatment for NAS (*Hudak, 2012; Osborn, 2010; Jansson, 2012*). Several treatment approaches are used and no universal standard of care exists among different institutions. Treatment approaches vary widely in terms of the pharmacological agent used, whether as a first-line or adjunct therapy. They also differ in the starting and maximal doses. As a general rule, however, medical management usually involves a rapid up-titration in dose to control symptoms, followed by a gradual weaning of typically 10% of the dose if signs of withdrawal allow (*Kraft, 2016*).

Recent evidence suggests that improved neonatal outcomes and Length of Stay (LOS) are best achieved through the adoption of, and adherence to, a stringent NAS treatment protocol (*Hall, 2014; Hall, 2015*). Methadone is chosen as the study drug in this trial as its pharmacokinetics have been studied in the neonatal population (*Wiles, 2015; Hall 2015*). In addition, methadone is ideal for our purpose given its mechanism of action and favorable adverse effects profile. Unlike the short half-life of morphine of 6.2 hours (*Lexicomp*) that requires dosing every 3 hours, the long half-life of methadone (19 +/- 14 hours in pediatric patients) (*Lexicomp*) allows for dosing every 12 to 24 hours, making it ideal for home therapy. Methadone is also approved by the FDA for narcotic withdrawal and has been widely used for both inpatient and outpatient management of NAS with no reported complications.

Home-based treatment:

According to Gregory (Gregory, July 2014), outcomes associated with the home-based approach were compared with those of the traditional inpatient hospitalized setting. The investigators found that *"providing detoxification in a home-based setting resulted in reduced hospital admission without prolonged exposure to medication and, for some infants, suggesting that the symptoms associated with NAS were managed effectively in the home-based setting."* Gregory further stated, *"Neonatal nurses seeking to develop and implement plans for care may adopt some best practices learned through the*

Transitional Care Model developed for older adults. Some of the essential elements of an effective Transitional Care Model that may be applied to the infant with NAS include the following:

1. *Use of a transitional care nurses to deliver and coordinate care for the infant with NAS within and across the healthcare settings;*
2. *Collaboration with family caregivers and team members in the implementation of a streamlined, evidence-based plan of care to promote positive health and cost outcomes;*
3. *Regular home visits by the transitional care nurse with available, ongoing telephone support (7 days per week);*
4. *Continuity of care between the hospital outpatient and primary care clinicians facilitated by the transitional care nurse;*
5. *Active engagement and education of family caregivers on all aspects of NAS."*

Methadone Demonstration Study:

This application is for a demonstration study, funded by the State of Florida Department of Health, using oral methadone to treat NAS both inpatient and outpatient in a specified infant population. The outpatient administration of oral methadone will be provided solely and directly by JHACH Kids Home Care registered nurses who are adequately trained and skilled in the recognition and management of NAS. Methadone will be administered at Operation PAR or at the parent home. Operation PAR, Inc. is a Detoxification Program Treatment Center in Largo Florida, and offers halfway housing as well as residential treatment options for clients in opioid treatment program. Operation PAR has agreed to assist in the identification of potential participants as well as allow JHACH Kids Home Care RNs to perform study related interventions at their site.

Current Experience with Procedures/Drugs:

JHACH operates one of Florida's largest neonatal intensive care units. With 97 beds, the JHACH NICU is dedicated to the outcomes of infants encompassing all types of illnesses from prematurity, neurological issues, surgical and medical needs, and neonatal abstinence syndrome (NAS). The staff in the NICU at JHACH (nurses and neonatal nurse practitioners) have been trained in the standardized scoring of NAS symptoms using the Modified Finnegan Neonatal Abstinence Severity Scoring tool (Finnegan, 3rd edition, pp. 1367-1378, 1992) and have been successfully applying it for the NAS population, averaging more than 100 infants per year. Even though morphine with clonidine adjunct therapy are the current standard of care at JHACH NICU, inpatient methadone was extensively and successfully used by JHACH for the treatment of NAS until 2010. The shift in protocol resulted from reasons unrelated to the effectiveness nor safety of methadone, and related instead to an attempt to modify the LOS.

This demonstration project will provide an opportunity to transition care of these infants to home, thus allowing for better care for the infant and improved neonatal outcome.

Other Relevant Information to Justify Research

Summary:

Research illustrates that early bonding between parent/caregiver leads to improved outcomes of the infant suffering from NAS. This demonstration projects allows for a greater participation of the mother in the care of her infant while inpatient. It will also empower her to better understand the nature of neonatal drug withdrawal, to recognize its signs in a timely fashion and to provide better non-pharmacological care for her infant with proven comfort and feeding techniques.

The project will also provide home support and close monitoring as well as regular developmental follow-up for these infants through our JHACH NICU follow-up clinic, hence identifying and quickly responding to delays. These infants are prone to have developmental issues and recent research is demonstrating they have problems upon entering the school systems at age 4 and 5 years. While we have follow-up clinics in St Petersburg and Sarasota, the current Medicaid system and Medicaid HMO's are not funding these infants to come to the clinics, as they are considering it primary care. JHACH NICU follow-up clinic is much different than primary care, is multidisciplinary and offers standardized psychometric testing and referrals for services as deemed indicated.

4. Inclusion/Exclusion Criteria for Mother/Baby dyad

Methadone Treatment Group:

Inclusion criteria

1) Baby is diagnosed with neonatal abstinence syndrome;
2) Mother under the care of Operation PAR;
3) Mother resides in Pinellas or Pasco county at the time of enrollment and is expected to throughout the infant's methadone treatment period;
4) Mother has been deemed by PAR officials as being compliant with the detoxification program;
5) Mother has completed induction methadone treatment and has had no changes in medication dosage of 10% or greater in the two weeks preceding delivery;
6) Mother has been prescreened and deemed adequate candidate by the demonstration project team members;
7) No known concerns from Florida Department of Children and Families (DCF) regarding the infant's ability to return to the home;
8) Newborns ≥ 37 0/7 weeks gestation;
9) Newborns transferred to JHACH within 72 hours from birth;
10) Newborns ≥ 2.5 kg weight at birth; Informed parental consent.

Exclusion Criteria

1) Major congenital anomalies;
2) Major concomitant medical illness including planned antibiotic treatment for greater than 3 days or NPO status;
3) Infants who are being placed for adoption;
4) Infants in significant pain requiring narcotic medication for comfort (for example those with a fracture);
5) Infants whose maternal UDS at the time of delivery is positive for any other drug of abuse beside opiates;
6) Mother with hearing or language impairment.

Comparison Group:

Inclusion Criteria:

1) Baby is diagnosed with neonatal abstinence syndrome;
2) Newborns ≥ 37 0/7 weeks gestation;
3) Newborns transferred to JHACH within 72 hours from birth;
4) Newborns ≥ 2.5 kg weight at birth;
5) Informed parental consent.

Exclusion Criteria:

1) Infant not requiring pharmacologic treatment for NAS;
2) Major congenital anomalies;
3) Major concomitant medical illness including planned antibiotic treatment for greater than 3 days or NPO status;
4) Infants who are being placed for adoption;
5) Infants in significant pain requiring narcotic medication for comfort (for example those with a fracture);
6) Mother with hearing or language impairment;
7) Infants known upon admission who will be placed into state custody or sheltered.

Study Procedures

a. **Study design, including the sequence and timing of study procedures** (distinguish research procedures from those that are part of routine care).

General Design Issues:

The proposed demonstration project is a non-randomized, un-blinded feasibility study. A prospective cohort study design will be implemented.

Eligibility and Enrollment Process:

a) Methadone Treatment Group: Mothers who meet the criteria for enrollment in the demonstration project will be identified by the Operation PAR personnel during the last month of pregnancy. Such Individuals will be approached by PAR personnel to determine their willingness to learn more about the methadone study. If they are interested, their contact information with be given to a study team member at Kids Home Care. The Kids Home Care study team member will contact the mother via telephone to discuss the study and may provide mother with a copy of the informed consent in order to give the mother ample time prior to delivery to ask questions of the study team.

JHACH NICU Stork Nurses communicate with the Bayfront Baby Place Nurses a minimum of two times per day to check for potential NAS infants and transfers. Such communication readily identifies candidate mother / infant dyads shortly after delivery, and the pre-qualified mother will be approached for consent by a member of the study team (MD or mid-level).

b) Comparison Group: Mothers of infants who are admitted to the JHACH NICU with the diagnosis of NAS and who are started on treatment with a narcotic different than methadone, will be identified during the first week of NICU admission. Those mothers will be approached for consent by a member of the study team.

The difference between the two groups is further delineated in the tables below.

> NOTE regarding screen failures:
> Up to 35% of infants with NAS do not require pharmacological treatment as their symptomatology is controlled by non-pharmacological interventions. Such infants are released home after an observation period of about 7 days. If a patient was consented for either the comparison or methadone group and did not require pharmacological treatment for NAS, these infants will be considered screen failures. Accordingly, there will be no measures of bonding and depression, no outpatient follow-up by either KHC or the JHACH pediatrician and no assessment of development.

Study Design:

Study Schedule of Events:

a) Methadone Treatment Group

Study Intervention	Enrollment	While inpatient	After discharge home on methadone	6 – 8 weeks of age	4 months of age	8 months of age	12 months of age
Informed Consent	X						
Methadone Administration		X[a]	X[b]				
Child Protective Investigator (CPI) clearance of the home		X (prior to discharge)					
Social Work Home Assessment			X (upon discharge)				
Face-to-face teleconferencing			X[C]				
Finnegan scoring		X	X[b]				
Kids Home Care Visit			X[b]		X[f]	X[f]	X[f]
JHACH Outpatient Pediatrician H&P, PE			X[d]				
The Postpartum Bonding Questionnaire (PBQ)		X[e]		X[f]			
Edinburgh Postnatal Depression Scale (EPDS)		X[e]		X[f]			
Ages And Stages Questionnaire (ASQ)					X	X	X

[a] Per protocol

[b] Twice daily until 48 hours after total weaning of medication is achieved

[C] Every 3-4 hours until 48 hours after total weaning of medication is achieved

[d] Within 1-2 days after discharge then weekly for 4 weeks until discontinuation of methadone treatment

[e] After initiation of methadone treatment and prior to discharge during the weaning phase of narcotic treatment

[f] Home visit or phone interview

Comparison Group:

Study Intervention	Enrollment	While inpatient	6 – 8 weeks of age
Informed Consent	X		
The Postpartum Bonding Questionnaire (PBQ)		X[a]	X[b]
Edinburgh Postnatal Depression Scale (EPDS)		X[a]	X[b]

[a] After initiation of standard of care narcotics for treatment of NAS and prior to discharge during the weaning phase of narcotic treatment

[b] Administered either through a home visit by Kids Home Care or via a phone interview conducted by a study team member

Routine (usual) care for infants born to mothers with a history of opiate use: All infants have routine scoring with the modified Finnegan scoring tool approximately every 3 to 4 hours per standard of care for signs of NAS. Infants will be managed with comfort, non-pharmacological measures. Initiation of medical treatment will take place when 2 consecutive Finnegan scores are > 8. Escalation of treatment and weaning will follow set protocols. Vital signs, blood pressures and cardiorespiratory monitoring follow the NICU standard of practice. Outpatient neurodevelopmental follow-up is offered at 1 and 2 years of age.

Comparison Group:

The comparison group of mother/baby dyads will receive standard of care treatment. The study interventions in this group are limited to the bonding and depression assessments. All other data required for analysis of the study aims can be abstracted from the baby's medical record as it is part of standard clinical care.

Methadone Treatment group:

A. Infant participants will receive the following services not part of the standard of care at JHACH:

a) Initiation of the commercially available methadone treatment instead of morphine as pharmacologic treatment (see methadone treatment below);
b) Maternal education on recognizing signs and symptoms of withdrawal as well as understanding and performing adequate Finnegan scoring. Specifically, mothers will be taught how to demonstrate tone and tremors on Physical exam.
c) Provision of close psychological and emotional support to mothers

d) Facilitation of prolonged maternal physical presence at her infant's bedside
e) Discharge home when stable on methadone treatment for continued home care. Stability is defined as 1) a maximal dose of methadone of 0.04 mg/kg at the time of discharge (Step 4 of Table 2), and 2) a history of successful weaning of methadone for a least 3 days prior to discharge;
f) Twice daily nursing visits in the home after discharge from the NICU for Finnegan scoring and administration of methadone along with general nursing assessment until 48 hours after total weaning of medication is achieved;
g) Provision of an electronic tablet to the mother to facilitate teleconferencing;
h) Face-to-face teleconferencing between the mother/infant and Kids HomeCare RNs versed in the care of NAS infants. Such virtual assessment will take place every 3-4 hours and will serve to obtain Finnegan scoring and assess infant. It will continue until 48 hours after total weaning of medication is achieved. After discontinuation of medication, Finnegan scores will be assessed when infant is awake and feeding (most of the Finnegan scoring items are obtained by history, assessment of infant's tone and tremors will be performed by the mother and witnessed by the nurses);
i) Social work home assessment upon discharge to the home. Child Protective Investigator (CPI) clearance of the home prior to discharge;
j) Follow-up home visit by the Kids Home Care RN 2 to 3 days after medical treatment is complete;
k) Follow-up with IRB approved study team JHACH Pediatrician, at his/her JHACH outpatient office 2 to 3 days after discharge home then weekly until 4 weeks after discontinuation of medication; If infant remains on medication for longer than a week after the initial pediatrician's visit, additional visits will be scheduled on a weekly basis until discontinuation of medication;
l) Home visit or phone interview by the Kids Home Care registered nurse at 4 months, 8 months and 12 months to screen development using Ages and Stages-based questionnaires (ASQ) (*Squires*, 1997).

B. Methadone treatment:

There is no agreed upon protocol of methadone dosing nor frequency of administration as recognized by the AAP. Protocols vary widely among institutions in the USA. The demonstration project methadone protocol utilized for this trial is loosely modeled on a protocol devised at Cincinnati Children's Hospital Medical Center based on pharmacokinetic data in a small patient population and subsequently implemented as the standard of care throughout the Cincinnati region (Table 1).

Initiation

- Initiate protocol for infants with 3 consecutive Finnegan scores ≥ 8, or 2 consecutive Finnegan scores ≥ 12.

	Methadone dose	Dosing interval	No. doses
Step 1	0.1 mg/kg	Every 6 h	4
Step 2	0.07 mg/kg	Every 12 h	2
Step 3	0.05 mg/kg	Every 12 h	2
Step 4	0.04 mg/kg	Every 12 h	2
Step 5	0.03 mg/kg	Every 12 h	2
Step 6	0.02 mg/kg	Every 12 h	2
Step 7	0.01 mg/kg	Every 12 h	2
Step 8	0.01 mg/kg	Every 24 h	1

Weaning

- Wean to the next step if the average Finnegan score is <8 for the past 24 hours.
- If the average Finnegan score is 8-12, do not wean.
- If the average Finnegan score is ≥12, consider an extra dose of methadone at the current step, or return to previous step.

Escalation

- If infant fails step 1 (score >12), consider steps 1A through 1C.

	Methadone dose	Dosing interval	No. of doses
Step 1A	0.1 mg/kg	Every 4 h	6
Step 1B	0.1 mg/kg	Every 8 h	3
Step 1C	0.1 mg/kg	Every 12 h	2

Adjunct therapy

- Consider adding phenobarbital if unable to wean for 2 consecutive days.

Discharge

- Observe for 72 hours from the last dose of step 8.

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The protocol is a refinement of a previous methadone protocol used as their standard of care. The revised protocol reduced the duration of drug treatment, as well as the total number of treatment doses, thus minimizing opportunities for drug ordering and medication errors (Hall, 2015). Infants tolerated the treatment protocol well with no significant adverse effects.

The rational for amending that protocol relates to the reported premature initiation of Phenobarbital as adjunct therapy. Most protocols call for the initiation of adjunct therapy when first line medication fails (i.e. reaching maximal doses or requiring multiple re-escalations of dosing). In Table 1 however, phenobarbital initiation happens instead during the weaning process. Accordingly, a rather large number of infants get started and discharged home on phenobarbital (22.6%).

Our goal is to introduce second-line treatment when truly indicated (i.e. when maximal safe therapy fails) and to minimize discharge home on medication, as this approach, while minimizing the LOS, allows for infants to remain on medication for an indeterminate length of time.

Demonstration Study Methadone Protocol

Initiation:

Initiate protocol for infants with 2 consecutive Finnegan scores > 8. Starting dose is 0.1 mg/kg/dose Q 6 hours (Table 2 - Step 1). As per hospital policy, medications may be given +/- 1 hour from scheduled administration time

Weaning:

Table 2. Initiation and weaning of methadone

Step	Methadone Dose (mg/kg)	Interval	Minimum Number of Doses
Step 1	0.1	Q6 h	8
Step 2	0.07	Q12 h	2
Step 3	0.05	Q12 h	2
Step 4	0.04	Q12 h	2
Step 5	0.03	Q12 h	2
Step 6	0.02	Q12 h	2
Step 7	0.01	Q12 h	2
Step 8	0.01	Q24 h	1

Initial weaning: wean after 48 hours of stable scores (i.e. 2 consecutive 24 hour Finnegan score averages < 8)
Subsequent weaning: Wean to the next step if the 24 hour Finnegan score average is < 8;
If the 24-hour Finnegan score average is 8-10, do not wean;
If the 24-hour Finnegan score average is ≥ 11, follow escalation below.

Table 2 Escalation:

- Escalation will take place by going back one step in the dosing regimen (i.e. go from Step 5 to Step 4, etc.)
- If infant needs escalation from Step 2 to Step 1, one may consider either going back up the one step to Step 1 or giving an additional methadone dose.
- Weaning will resume after 24 hours of stable scores (i.e. a 24 hour average of <8)
- If infant fails Step 1 above, increase interval of dosing to Q 4 hour (Step 1A in table 3 below)

If infant has 2 consecutive Finnegan scores that indicate severe withdrawal symptoms, despite non-pharmacological intervention, the PI or a co-Investigator needs to be informed. The PI or a co-investigator physician will assess each situation based on infant's medication dosage, its frequency and timing of administration, and one of the 3 following options will be offered: 1) re-escalate to the previous step; 2) consider giving an additional dose of methadone if > 4 hours before the next scheduled dose and 3) consider moving up the next scheduled dose without escalation.

Weaning after Step 1 escalation (steps 1A through 1C)

Table 3. Methadone escalation after weaning failure			
Step	**Methadone dose (mg/kg)**	**Interval**	**Minimum Number of doses**
Step 1A	0.1	Q4 h	6
Step 1B	0.1	Q8 h	3
Step 1C	0.1	Q12 h	2
Weaning: Wean to the next step if the 24 hour Finnegan score average is < 8; If the 24-hour Finnegan score average is 8-10, do not wean; If the 24-hour Finnegan score average is ≥ 11, follow escalation below			

Table 3 Escalation:

- If patient's dosing interval has to be escalated to table 3, weaning will follow as delineated in the table.
- If infant needs escalation from Step 1B to Step 1A, one may consider either going back up the one step to Step 1 or giving an additional methadone dose.
- Once infant weans to Step 1C, further wean will be to table 2, Step 2. Weaning will then follow the protocol for table 2.

Slight variation in timing of drug administration is inherent in the provision of medical care. JHACH policy allows for drugs to be administered by nursing staff within +/- 1-hour of the scheduled timing.

Differences between Table 1 and Table 2:

As mentioned above, this modified protocol allows for initiation and weaning indications that are more in line with the AAP recommendations and the JHACH culture of minimizing infant's discomfort and providing medication weaning in a safe and conservative fashion (Table 2).

The differences between tables 1 and 2 pertain to the following:

1) Finnegan scores that initiate treatment: 2 consecutive scores > 8 instead of 3 scores of ≥ 8
2) 24-hour Finnegan score averages to guide weaning, observation and re-escalation:
   - wean if the average is <8
   - observe if average 8-10, instead of 8-12
   - re-escalate for average ≥ 11 instead of ≥ 12
3) Observe a 48-hour (instead of 24) of stable scores prior to initial weaning and prior to wean after re-escalation if patient falls in table 2.

C. Discharge home:

Infants will be discharged home or to Operation PAR when they are deemed stable by the treating team.

Stability is defined as:

1) A maximal dose of methadone of ≤ 0.04 mg/kg at the time of discharge (Step 4 of Table 2), and
2) A history of successful weaning of methadone for a least 3 days prior to discharge, and
3) No dose re-escalation in the previous 72 hours prior to discharge.

Timing of medication administration may be changed gradually prior to discharge, as allowed by hospital policy, to accommodate outpatient administration by Kids Home Care.

Weaning at home will follow the weaning protocol delineated above. Finnegan scoring will be continued at home. It will be done twice daily by the visiting Kids Home Care RN. Virtual Finnegan scoring assessment will be done as described above every 3 to 4 hours by teleconferencing with the Kids Home Care RN versed in the care of infants with NAS.

D. Discontinuation of methadone*:*

Methadone will be discontinued when the dose is 0.01 mg/kg/dose every 24 hours and the previous 24-hour average if ≤ 6.

E. Home observation post discontinuation of methadone:

Observe infant for 72 hours off medication with twice daily nursing visits. Treatment is considered successful if infant's 24-hour average remains < 8.

This observation period is important as it allows to watch for possible rebound of symptomatology after cessation of medical intervention, and is in accordance with the standard of care that infants with NAS receive at JHACH. If during this observation period infants develop rebound symptomatology (defined as a 24 hour Finnegan score average of > 8), the nurse will institute appropriate measures of comforting infant and reducing / eliminating noxious stimuli. If comfort measures fail and Finnegan scores remain > 8 on 2 consecutive assessments performed at 3-4 hour intervals, methadone will be resumed at the last dose that infant received prior to discontinuation. Further Re-escalation and weaning will be performed per initial protocol.

F. Pediatrician Follow-up:

It is standard of care for infants discharged from the JHACH NICU to see their primary care provider (PCP) within a day or two of discharge. Follow-up will be provided by an IRB approved study team JHACH Pediatrician, and will take place within one or two days after discharge then weekly for 4 weeks after discontinuation of methadone treatment.

G. Off-treatment Criteria*:*

Off-treatment is defined as an infant who no longer qualifies for discharge home on methadone – i.e. requiring adjuvant pharmacological therapy or re-admission to the hospital while still on methadone

1. **Addition of adjuvant therapy:**

   It is common for infants suffering from NAS to require the addition of an adjunct therapeutic agent for control of symptoms. This second-line agent varies among institutions but consists often of phenobarbital.

   If demonstration project participants have uncontrolled NAS symptoms (defined as a 24-hour Finnegan score average ≥ 11 despite comfort measures and maximal methadone dosing – i.e. 0.1 mg/kg given every 4 hours), the infant will be placed on phenobarbital, the standard of care at JHACH NICU. Such infant will be off-treatment from the study i.e. will not qualify for subsequent discharge home prior to discontinuation of methadone. Maternal assessments of bonding and depression will remain ongoing. There will be no home nursing visits.

2. **Re-admission to the JHACH NICU:**

   It is common for infants suffering from NAS not to tolerate weaning off medication. Re-escalation during that phase is common. If during the weaning phase, infant's Finnegan scores are > 8 on 2 consecutive scores despite comfort measures, the dose of methadone will be increased to the previous dose at which the patient's symptoms were well controlled.
   If an infant requires consecutive re-escalation of medication with no control of symptoms (i.e. 24 hour Finnegan scores > 6), such infant will be re-admitted to the hospital.
   - for infants who were discharged home on a dose of methadone that is < 0.04 mg/kg, such infant will be re-admitted to the hospital if consecutive re-escalation of methadone are required and infant reaches a dose of 0.05 mg/kg.
   - for infants discharged home at a dose of 0.04 mg/kg, who do not tolerate weaning at home and who require dose escalation, the dose will be increased in 2 increments per protocol to a value of 0.07 mg/kg before re-admission to the hospital.

   Upon re-admission to the JHACH NICU, such infant will no longer qualify for discharge home while on methadone medication and will be considered off-treatment. There will be no further home nursing visits. Analysis of maternal assessments of bonding and depression will remain ongoing.

Study related questionnaires to assess bonding and depression:

A. The Postpartum Bonding Questionnaire (PBQ) and the Edinburgh Postnatal Depression Scale (EPDS) will be given to mothers of methadone-treated and non-treated infants at 2 different time points:

i. After initiation of methadone and prior to discharge during the weaning phase of narcotic treatment and
ii. At 6 to 8 weeks. The 6 to 8 weeks questionnaires will be administered either through a home visit by Kids Home Care or via a phone interview conducted by a study member

B. Safety plan for handling survey responses related to the Postpartum Bonding Questionnaire:
Dr. Lacy Chavis, a licensed psychologist and Co-Investigator on this study, will oversee the interpretation of the questionnaire as this is her area of expertise. If Dr. Chavis is not available, Dr. Aja Meyer (licensed psychologist) will oversee the interpretation of the questionnaire. For the PBQ, scores are summated for each factor, with a high score indicating concern for bonding. Any woman who reports a high score on any of the factors (greater than 11 for factor 1, greater than 16 for factor 2, greater than 9 for factor 3, or greater than 2 for factor 4) will be counselled about the results by a clinical social worker, part of the study team. The counselling will happen no later than 24 hours after the mother is identified. The study member will contact the woman, will suggest that she seeks further care, and will provide her with the name and telephone number of resources in the community to seek further follow-up. In addition, the social worker will ask the woman whether she may share this information with her obstetrician to help her better manage her obstetrical care. (All women have signed a HIPAA authorization upon enrollment). If she agrees, the treating obstetrician will be notified. A social worker pre-identified by operation PAR will be notified as well within 24 hours of identifying bonding-related concerns.

C. Safety plan for handling survey responses related to the Edinburgh Postnatal Depression Scale:

Dr. Lacy Chavis, a licensed psychologist and Co-Investigator on this study, will oversee the interpretation of the questionnaire as this is her area of expertise. If Dr. Chavis is not available, Dr. Aja Meyer (licensed psychologist) will oversee the interpretation of the questionnaire. For the EPDS questionnaire, a score of 10 or greater , as well as any answer choice other than "never" on question #10 of the EPDS) are indicative of *depressive symptomatology*. Any woman identified as being depressed will be counseled about her mental health by a licensed social worker, part of the study team. The counselling will happen no more than 24 hours after she is identified. The social worker will contact the woman, will suggest that she seeks further care, and will provide her with the name and telephone number of mental health resources in the community to seek further follow-up. In addition, the social worker will ask the woman whether she may share this information with her obstetrician to help her better manage her obstetrical care. (All women have signed a HIPAA authorization upon enrollment). If she agrees, the treating obstetrician will be notified. A social worker pre-identified by operation PAR will be notified as well within 24 hours of identifying depression-related concerns.

If the mother does indicate that she has hurt her baby, an immediate call to the Department of Children and Families (DCF) will also be made.

Study related questionnaires to assess infant development:

Infant development will be assessed at 4, 8 and 12 months of age using the Ages and Stages Questionnaire (ASQ). The questionnaires are screening tools designed to identify infants at risk for developmental delays through caregivers' provision of quantitative information regarding their infant's development. The questionnaires will be administered by a study member either through a home visit or via a phone interview. The questionnaire will be reviewed and interpreted by Dr. Lacy Chavis. If delay is suspected or identified, the infant's pediatrician will be notified with the mother's approval to provide further follow-up.

Study duration and number of study visits required of research participants.

Accrual:

JHACH admitted and average of 131 NAS infants in recent years who required pharmacological treatment for NAS. Approximately 30% of those mother/infant dyads were residents of PAR. We anticipate to enroll 25 mother/baby dyads into the methadone treatment group and 25 mother/baby dyads into the control group for a total of 100 participants. Both the mother and infant are research participants. Those infant participants are defined as 1) needing methadone or other opiate treatment, 2) transitioning to home care, and 3) successfully weaning off medication.

This number has been extrapolated taken into account the following projections/assumptions: 1) not all mothers staying at PAR will meet criteria for participation, and 2) polydrug use may be discovered at the time of delivery thus excluding from participation, and 3) 20-40% of infants enrolled may need adjunct second line therapy.

b. **Blinding, including justification for blinding or not blinding the trial, if applicable**.

This is a demonstration study with no blinding of subjects involved.

c. **Justification of why participants will not receive routine care or will have current therapy stopped.**

All infants will continue to receive routine hospital care. Methadone treatment is approved by the FDA, and endorsed by the AAP for inpatient and outpatient treatment of infants with NAS. While methadone is not used as the standard of care at JHACH NICU for infants with NAS at birth, it is still used for later iatrogenic withdrawal in the NICU and other intensive care units in the hospital.

d. **Justification for inclusion of a placebo or non-treatment group.** N/A Will need to justify this as a comparison groups has been included

e. **Definition of treatment failure or participant removal criteria.**

As delineated above, infants will be off-treatment from the demonstration project if 1) they require the addition of a second-line of pharmacological treatment or 2) they require re-admission to the

hospital. Data will still be collected until final hospital discharge for these infants and the maternal assessments of bonding and depression will remain ongoing. .

Other Indications for participant off-study:

a. Parent withdraws informed consent at any time
b. Infant transfers to another hospital.
c. Infant experiences an unexpected adverse event deemed related to study intervention

f. Description of what happens to participants receiving therapy when study ends or if an infant's participation in the study ends prematurely.

If an infant is prematurely removed from the study, standard of care treatment will resume until discharge.

5. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used. Commercially available methadone will be used for this study. Methadone is routinely used for the management of NAS at various institutions. Its efficacy has been shown in a number of studies and has been endorsed by both the FDA and the AAP for inpatient and outpatient treatment of infants.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. While the methadone label does not explicitly state approval for use in neonates, the use of methadone in the neonate population is widely used at various institutions for opiate withdrawal. This study uses commercially available methadone. This trial is exempt from the IND requirements since it meets all the following FDA IND Exemption criteria per 21 CFR 312.2(b):

- The drug product is lawfully marketed in the United States;
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent;
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

c. **Justification and safety information if non-FDA approved drugs without an IND will be administered.** N/A

6. **Study Statistics**

Study related variables will be collected, entered in REDCAP, and maintained confidential.

a. **Primary outcome variable:** Length of Stay (LOS)

b. **Additional outcomes of interest to be examined:**

1) Maternal bonding measured by the Postpartum Bonding Questionnaire (PBQ);
2) Depressive symptomatology measured by Edinburgh Postnatal Depression Scale (EPDS);
3) Hospital readmission within 30 days;
4) Weight gain of greater than 15% above Birth Weight at 30 days of age;
5) Age appropriate development as screened by the Ages and Stages questionnaires.

c. **Statistical plan including sample size justification and interim data analysis:**

Demographic and clinical characteristics of participants will be summarized using means with standard deviations (SD) or median with interquartile ranges for continuous variables and counts and percentages for categorical variables. The primary outcome, length of stay, will be summarized using mean (SD) or median and interquartile range and will be compared to the comparison group using the t-test or Wilcoxon rank sum test as appropriate. For the secondary outcomes, the scores on the postpartum bonding questionnaire or the Edinburgh Postnatal Depression Scale will be summarized using means (SD) and compared to other patients in the comparison group using independent two-sample t-test. The proportion of participants that are readmitted within 30 days or with a weight gain of greater than 15% above birth weight will be compared to the comparison group using a Chi-squared or Fishers exact test as appropriate. Among the methadone cohort, we will calculate percentage of infants with age appropriate development at 4, 8 and 12 months. We anticipate that 25 mother-child dyads in each group will be available for the study. We expect that the mean LOS in the comparison group will be around 25 days (based on historical data). This sample size will allow us to estimate differences in LOS of >4 days with sufficient power (80%) at an alpha of 0.05, assuming a standard deviation of 5 days for both groups.

Early stopping rules:

Infant: requiring therapy with a second drug

Parents: desire to remove the infant from the study at any time or when infant is transferred to another hospital.

7. **Risks**

a. **Medical risks, listing all procedures, their major and minor risks and expected frequency:**

Risks include the possibility of unexpected toxicity from methadone. Methadone is a narcotic and as with all drugs in this class, respiratory depression may occur; however, it is less likely because the infants are already tolerant to opiates from *in-utero* exposure. The routine treatment for NAS infants at JHACH is oral morphine, a pure mu receptor opioid agonist. In comparison to morphine, methadone is in addition an N-methyl-d-aspartate agonist with a long half-life. Infants are routinely closely monitored during the initiation and escalation phases of treatment. Studies have failed to show any additional risk of respiratory depression of methadone as compared to oral morphine. In addition, the half-life of methadone makes it less likely for its cessation to result in acute symptomatology.

Other infrequent side effects may include rashes and feeding problems. Rashes from drugs are uncommon in babies. Feeding problems including uncoordinated sucking and swallowing are common in infants who are withdrawing from narcotics. The scoring system used to monitor the babies includes monitoring both excess sleeping with poor wake-alert feeding cycles and infant feeding ability scales to allow for appropriate adjustments of dosing thus minimizing these side effects.

b. Steps taken to minimize the risks:

The infants will be closely monitored for the following: heart rate, respiratory rate, temperature, oxygen saturation and blood pressure in the NICU during the initiation and escalation of methadone. All infants in the JHACH NICU have routine continuous oxygen saturation monitoring and also have continuous cardiorespiratory monitoring as standard of care. The usual medication for reversal of acute opioid overdose is naloxone. However with chronic opioid use this reversal is contradicted because it would precipitate acute narcotic withdrawal. Instead supportive care would include atropine if needed for bradycardia, intravenous fluids and vasopressor agents if needed for hypotension and ventilator support if needed for inadequate respiration.

All records are confidential. The data sheets are coded such that personal identifiers are omitted. Consent forms are in the infant's chart and copies are locked in the office of the PI.
Safe Dispensing of Study Drug: The investigational research pharmacy at JHACH is directing the dosing and distribution of the methadone through a locked and password coded drug-dispensing system (as is routine for opiates). Home use of methadone is regulated by the FDA and the State of Florida.

Adverse Events
An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

- Adverse events will only be collected on those participants who receive demonstration study drug
- This study will only capture adverse events (AE) that meet at least ONE of the following criteria:

- The AE is at least possibly related to the demonstration study drug AND is unexpected in nature or severity
- The AE is a serious adverse event (SAE) as defined below*.
- The AE is one of the following adverse events of interest:
  - Respiratory depressions (respirations < 20/min by auscultation)
  - Bronchospasm
  - Angioneurotic edema
  - Anaphylactic shock
  - Need for respiratory support
  - Cardiovascular compromise requiring fluid replacement

The following will be collected and/or accessed for each adverse event:

- AE Start date and stop date
- AE Severity: mild, moderate, or severe
- AE relatedness to study drug: unrelated, possibly related, probably related, or definitely related
- AE expectedness: An adverse event is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity or severity that has been observed.
- AE seriousness: An adverse event is considered a Serious Adverse Event (SAE)* if it results in one of the following outcomes:
  - Death
  - A life-threatening adverse event (an adverse event is considered "life-threatening" if its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
    Or another important medical event that may not have resulted in death, been life-threatening, or required hospitalization, but nonetheless still considered serious when, based upon appropriate medical judgment, the event jeopardized the patient or subject and may require medical or surgical intervention to prevent one of the above outcomes listed in this SAE definition

Adverse Event Reporting Requirements:

Any safety-related event meeting the JHM IRB's definition of an unanticipated problem will be appropriately documented, reported, and followed per institutional policies.

c. Plan for reporting unanticipated problems or study deviations:

All adverse events that meet the criteria of an Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO) will be reported by the PI or designee to the JHM IRB per JHM IRB policy. A master cumulative Protocol Deviation log will be used by the PI and study team to log all study deviations and will be reported to the IRB per institutional policies.

d. Data Safety and Monitoring Plan:

Data safety and monitoring will be done by a JHACH pediatrician (Heinz Chavez, MD) who is experienced in the care of sick newborns. He is independent from the investigative team. His primary focus will be on drug related toxicity and protocol adherence. Dr. Chavez will review the protocol at staged points as follows:

1) Prior to the start of the trial
2) After accrual of the first 50% (n=13) of infants treatment in the methadone treatment group
3) After accrual of the second 50% (n=12) of infants treatment in the methadone treatment group
4) At the completion of the trial

Stopping for harm will be done at the judgment of Dr. Chavez, as the data safety monitor, taking into account the seriousness and estimated excess risk of any observed adverse effects and the strength of the statistical evidence for the adverse effects.

Along with Dr. Chavez, everybody on the research team will be adherent to strict safety parameters and will be monitoring for moderate and severe cardiorespiratory events that require positive pressure ventilation and/or fluid resuscitation as intervention.

Stopping procedures were computed using the sequential probability ratio test (SPRT) with alpha set at .05 and power at 80%. Adverse events were examined based on three categories of (1) severe, (2) moderate requiring oxygen or room air flow, and (3) moderate requiring tactile stimulation. Using baseline rates of 8%, 13%, and 8%, accordingly for categories 1 through 3 above, and excessive rates of 13%, 25%, and 17%, accordingly, stopping procedures were calculated as follows:

- Severe AE
- Moderate AE (oxygen/flow)
- Moderate AE (tactile stimulation)

1) Using baseline rate of 8% and excessive rate of 13%, the first 5 events would not stop the trial. But the following would require a stop:
   - If 6 of the first 8 patients have a severe adverse event
   - If 7 of the first 17 patients have a severe adverse event
   - If 8 of the first 27 patients (goes out of our sample size) have a severe adverse event

2) Using baseline rate of 13% and excessive rate of 25%, the first 4 events would not stop the trial. But the following would require a stop:
   - If 5 of the first 8 patients have a moderate adverse event requiring oxygen/flow
   - If 6 of the first 13 patients have a moderate adverse event requiring oxygen/flow

- If 7 of the first 18 patients have a moderate adverse event requiring oxygen/flow
- If 8 of the first 24 patients have a moderate adverse event requiring oxygen/flow

3) Using baseline rate of 8% and excessive rate of 17%, the first 3 events would not stop the trial. But the following would require a stop:
   - If 4 of the first 6 patients have a moderate adverse event requiring tactile stimulation.
   - If 5 of the first 14 patients have a moderate adverse event requiring tactile stimulation.
   - If 6 of the first 22 patients have a moderate adverse event requiring tactile stimulation
   - If 7 of the first 30 patients (goes out of our sample size) have a moderate adverse event requiring tactile stimulation.

   For this trial we define "unsafe" if the use of methadone is associated with frequency of moderate or adverse cardiorespiratory events that requires an intervention that exceeds a specified thresholds outlined above that is sufficient to stop the trial. Thus unsafe and stopping parameters should be the same in this small trial.

e. Legal risks such as the risks that would be associated with breach of confidentiality:
N/A

f. Financial risks to the participants:

N/A

8. Benefits

a. Description of the probable benefits for the participant and for society:

Participation has the potential benefit of reducing the length of hospitalization for infants withdrawing from *in-utero* acquired narcotic dependence. Decreasing the duration of hospitalization would interfere less with family bonding, decrease the potential for nosocomial infections and decrease cost.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Infants enrolled in the methadone treatment group will receive methadone at no charge. Families enrolled in the methadone treatment group and cleared for discharge home will receive upon discharge from the hospital the following: 1) A mamaRoo swing, and 2) 3 halo sleep sacs. In addition, they will receive a $10 gas card for each of the anticipated 5 pediatrician office visits.

10. Costs

There are no additional costs to participants in this study.

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