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Therapeutic Management and Neurobehavioral Outcomes of Neonatal Abstinence Syndrome

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GENERAL INFORMATION

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Approved modifications not specifically noted in protocol v05.15.18

Date	Modification summary	Modification summary	Modification summary
6/8/18	Incorporate home visits for outcomes assessments/alternate contact	Add “Ages and Stages” to follow up assessments	Practical extension for signed consent (~30 hrs post birth)
6/27/19	Clarification of prisoner exclusion as per Prisoner Certification OHRP	OHRP acknowledgment of Prisoner Certification (8/1/19)	
3/13/20	As per UMCCTS_IRB Covid-19 study restrictions, halt enrollment, all in-person bedside studies, all in-person study visits; followup via phone; adhere to state and site safety requirements.		
8/20/20	State and respective site/Institutional Covid-19 safety protocols to resume in-person studies; adhere to state and site safety protocols; hybrid followup.		
12/7/20	Closed enrollment due to unanticipated move of PI, required study close-out at primary Institution, and untimely reduction in study personnel.		

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List of Abbreviations

COI	Conflict of Interest
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EMSM	External Medical Safety Monitor
IRB	Institutional Review Board
NAS	Neonatal Abstinence Syndrome
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Events
SAR	Suspected Adverse Reactions
SCC	Standard Clinical Care
SVS	Stochastic Vibrotactile Stimulation

1 BACKGROUND

Neonatal Abstinence Syndrome (NAS) refers to a variety of withdrawal symptoms, particularly prevalent in newborns with opioid exposure. Clinically significant neurobehavioral symptoms include pathophysiological cardio-respiratory instabilities, gastrointestinal dysfunction, hypersensitivity, and sleep disruption. There is a critical need to develop non-pharmacological interventions for managing withdrawal in newborns to reduce withdrawal symptoms, facilitate weaning, decrease pharmacotherapy, and provide additional intervention for infants in whom pharmacological treatment is insufficient. Growing research suggests the importance of sensory tactile stimulation for promoting physiological maturation, brain development, and stability of function, and for improving behaviors implicated in intrauterine drug exposure. Evidence supports that low-level, stochastic (random) stimulation can promote stability in destabilized biological systems, including improved transduction of cutaneous mechanoreceptors in animals, sensory perception in adults, and improved cardio-respiratory function in premature infants. Our recent pilot data suggests that acute presentation of low-level stochastic vibratory stimulation (SVS) delivered through a uniquely-constructed crib mattress improves physiological function in drug-withdrawing infants. We hypothesize that stochastic resonance may affect somatosensory and vestibular systems by facilitating more accurate detection of sensory inputs (e.g., touch, auditory) and increase neural stability. For example, SVS may stimulate pressure receptors to improve vagal tone and cardiac activity, and impinge upon respiratory oscillators to enhance respiratory function. The main objective of this proposal is to test whether early intervention (initiated within 24 hours post birth) and daily administration of SVS reduces withdrawal and improves neurobehavioral outcomes.

1.1 Trial Objectives

This study investigates Stochastic Vibrotactile Stimulation (SVS) complementary to standard of care for treating NAS. Using a specially-constructed crib mattress we will determine if SVS reduces symptoms and duration of NAS and improves long term outcomes in intrauterine opioid-exposed newborns. Findings from this study will elucidate whether SVS has potential as a therapeutic treatment for drug-exposed newborns to reduce symptomatology, facilitate weaning and minimize hospitalization, with implications for better regulation of systems and improved developmental outcomes.

1.1.1. Specific Aims. The three areas to be investigated in this project are:

Specific Aim 1. Determine the efficacy of SVS as a non-pharmacological therapy complementary to standard clinical care (SCC) for reducing severity and duration of opioid withdrawal in newborns compared to SCC alone. Quantify clinical variables: NAS severity/administration of treatment, treatment days, days in hospital, velocity of weight gain, cumulative morphine dose, and longitudinal assessment of movement activity.

Specific Aim 2. Examine physiological responses to SVS compared to SCC at two stages of withdrawal severity. Measure cardio-respiratory stability, temperature regulation, and movement activity.

Specific Aim 3. Compare neurobehavioral outcomes in fetal drug-exposed infants between infants who received SVS and those who received SCC. Examine longitudinal outcomes assessments at 1 month, 6-months and 1 year to test whether early intervention with SVS compared to SCC improves physical, social, emotional and cognitive development.

2 SUMMARY OF THE PROTOCOL

2.1 Brief Description of the Protocol (Study Design)

The proposed experiments aim to examine whether SVS, using a specially-designed crib mattress, has potential as a complementary treatment of NAS. We will determine if SVS reduces NAS severity (administration of treatment/treatment days), cumulative morphine dose and days in hospital, reduces specific physiological markers of withdrawal (excessive movement and cardio-respiratory instabilities), and improves neurodevelopment outcomes in the first year of life.

NOTE: All changes to the protocol must be approved by NIDA prior to implementation.

2.1.1. Investigational Device. ***Stochastic Vibrotactile Stimulation (SVS).*** The infant's crib mattress will be replaced with a specially constructed mattress (non-commercially available) to provide gentle vibrations and sounds during mattress stimulations. The mattress is embedded with mechanical actuators that provide whole-body SVS (30-60Hz; ~10-12μm RMS). Co Fab Design, LLC will construct the mattresses and drivers as per the design documents furnished under Confidentiality Disclosure Agreement (CDA; University of Massachusetts Medical School/Wyss Institute-Harvard University patent: PCT/US2015/021999) for research purposes only as per the licensed mattress assembly and electrical assembly and verification documentation; device components may be modified with improved technologies that provide equivalent mattress output to help ensure consistency of mattress integrity over time. Engineers from the Wyss Institute and the University of Pittsburgh will provide assistance in the build to ensure it performs as per the original patent documentation.

2.1.2. Study Design/Type. This study is a randomized, placebo-controlled, parallel group clinical trial. Eligible patients will be randomized into one of two groups in a 1:1 ratio, matched for gender, to either (1) SVS or (2) SCC:

1) <u>SVS</u>. Experimental Intervention: Newborn infants at-risk for NAS due to opioid exposure *in utero* randomized to this arm will receive daily intervals of continuous SVS (ON) and no SVS (OFF) throughout hospitalization, starting within 30-hrs post birth. An automated control box will be set to deliver continuous alternating 3-hr cycles of ON/OFF intervals. A stimulation period will always be followed by an interval of no stimulation; in any 24-hr period an infant will not receive more than a total of 12 hrs of stimulation (should the infant remain in the crib throughout an entire 24 hr period). Notably, infants are not always in their crib and it is not feasible to provide round-the-clock research staffing to monitor when the infant is in or out of the crib (e.g., being held

by caregiver, fed, in motorized bedside glider – all part of the standard of care). The pre-programmed 3-hr duty cycle, 24/7, affords opportunity to capture periods when the infant is in the crib, and also conforms to routine timing of medication. Periods of stimulation will be complementary to standard of clinical care (e.g., clinically-determined pharmacological management; routine holding by caregiver or hospital-issued motorized glider; breast and/or bottle feed). A bedside log will indicate periods the infant is in the crib, being held, or placed in hospital-issued gliders/motorized seats. Infants will be scored for severity of withdrawal using standardized, modified Finnegan scoring system by clinical-care nurses per routine clinical care throughout hospitalization, and may receive pharmacological treatment as per standard care determined by the medical-care team at the respective institution.

2) SCC. No Intervention: Standard of Clinical Care (SCC). Newborn infants at-risk for NAS due to opioid exposure in utero randomized to this arm will be enrolled within 30-hours post birth and receive standard of care (e.g., clinically-determined pharmacological management; routine holding by caregiver or hospital-issued motorized glider; breast and/or bottle feed). Infants will be issued a hospital crib mattress. A bedside log will indicate periods the infant is in the crib, being held, or placed in hospital-issued gliders/motorized seats. Infants will be scored for severity of withdrawal using standardized, modified Finnegan scoring system by clinical care nurses per routine clinical care throughout hospitalization, and may receive pharmacological treatment as per standard care determined by the medical-care team at the respective institution.

2.1.3. Study Site. Studies will be conducted at the UMass Memorial Healthcare Neonatal Intensive Care Unit (NICU), Continuing Care Nursery (CCN), and Newborn Nursery (NN) – referred to as UMass - and at the Magee-Women's NICU and Well-Baby Nursery, and Mercy Hospital, of the University of Pittsburgh Medical Center – referred to as UPitt - where infants receive round-the-clock medical care. Studies for Aim 1 and Aim 2 will be performed at the infant's hospital bedside, outcome assessments for Aim 3 will be performed at respective hospital inpatient (if infant still hospitalized) and outpatient facilities.

2.1.4. Study Duration. Subjects will participate in the study throughout their hospitalization, beginning within 30 hours post birth, and will be followed for up to 14 months post post-hospital discharge via medical records, telephone interviews, and return visits for outcome assessments***.***

***2.1.5. Randomization*.** Random allocation of subject to treatment (SVS or SCC) will involve a permuted block design with random block sizes to assure equal treatment assignment for both treatments. We will stratify the randomization process by clinical site to force a balance between treatment groups and gender within each site. The random treatment assignments will be generated in SAS and uploaded into the IVRS system. The randomization process will verify patient eligibility before issuing treatment assignment. Treatment assignments will be in the form of mattress assignment tracked by the IVRS system based on admission and discharge information entered into REDCap (**See 4.2 below**). The IVRS system can be accessed by certified study staff

either through a telephone call or over the internet to a secure web site. The treatment assignments are recorded automatically in the REDCap system through an interface between the two systems and cannot be modified once imported from the IVRS system. The randomizations are monitored and verified by study staff on a routine basis. The IVRS also will monitor mattress availability and will notify study staff if a mattress of each type is not available for a randomization. (Maternal exposure will be stratified in the analysis).

2.2 Primary and Secondary Outcome Measures

Table 1: Primary and Secondary Study Endpoints.

	Aim 1 Primary Clinical Outcomes	**Aim 1 Longitudinal Physiological Outcomes**	**Aim 2 Acute Physiological Outcomes (UMass only)**	**Aim 3 1-Year Follow-Up Assessment Outcomes**
Outcome Variables	NAS Severity Scores (trajectory: daily averages and max scores) Weight Gain/ Head Circumference (trajectory: daily measures) Pharmacotherapy: admin, type, dose (cumulative dose/normalized for body weight) Hospital Duration: Day of life infant is discharged from hospital (length of stay)	Movement Activity: 12 and 24 hr assessments actigraphy (averages: trajectory; frequency; index of sleep)	Movement Activity (frequency and duration; histograms): Index of irritability and sleep disruption/fragmentation Cardio-Respiratory control (mean/histograms: respiratory rate, frequency distribution; heart rate, frequency distribution) Other NAS Symptomatology: Temperature/Oxygenation (mean)	Environmental and Family Function (1-6-12 mo) Functional Status (1-6-12 mo) Neurodevelopment (1-6-12 mo) Behavioral and Emotional Status (6 and 12 mo) Parent Intellectual Ability (1 x assessment) Brief Infant Sleep Questionnaire (1-6-12mos)

Table 2: **Neurobehavioral Assessments**.

Task (time) Testing Age	Description and respondent [Child (C) or parent (P)]	Key Variables
Functional Status of Infant		
GOS-E Peds[59] (10') **1mo, 6mo, and 12mo**	The 8 GOS-E Peds categories track recovery of function between groups. This version includes semi-structured interview questions relevant to infants. Administered by Outcomes Specialist. (C, P) (Upload: Pcori-GOS).	**Category score (1-8)**
Pediatric Quality of Life[58] (5') **6mo and 12mo**	The PedsQL Parent Report for Infants is available for age ranges from 1 to 12 months. Scales assess physical function, physical symptoms, emotional function, social function, and cognitive function. Administered by Outcomes Specialist or Research Study Staff. (P) (Upload: Peds QL)	**Total score**; Subscale scores
Neurodevelopment and Sleep Status of Infant		
Bayley Scales of Infant & Toddler 3rd Ed.[60] (30') **6mo and 12mo**	The Bayley iii measures neurodevelopment to 3 yrs. Provides measures of cognitive function: visual preference, attention, memory, sensorimotor, exploration, manipulation, concept formation. Fine and gross motor development are also assessed. Administered by Outcomes Specialist. (C) (Upload: Bayley Record Form)	**Cognitive & Motor Scores;** Subtest scaled scores
Pediatric Evaluation of Disability Inventory[61] (10') **6mo and 12 mo**	The PEDI Mobility domain provides a standardized assessment of mobility skills appropriate for children up to the age of 4 years. Administered by Outcomes Specialist or Research Study Staff. (C) (Upload: Pedi Self Care and Mobility)	**Mobility Score**
Brief Infant Sleep Questionnaire (Sadeh, 2004) **1mo, 6mo, 12mo**	The BISQ is a modified questionnaire that provides a general assessment of infant sleep behaviors. Administered by Outcomes Specialist or Research Study Staff. (P) (Upload modified BISQ)	**General Sleep Assessments**
Behavior & Emotional Status of Infant		
Bayley Social and Emotional Scale[60] (10') **6mo and 12 mo**	The Bayley S&E measures emotional adjustment of infants and toddlers. Administered by Outcomes Specialist*. (P) (Upload Bayley Social and Emotional Scale)	**Composite Score**
Parent Intellectual Ability and Psychological Status		
Wechsler Abbreviated Scale of Intelligence[57] (20') ***1mo**	The WASI ii is a short and reliable measure of intelligence in clinical, psycho-educational, and research settings and is individually administered. 2 subtests will be used to generate a FSIQ: Vocabulary requires individual to define words of increasing difficulty; Block Design assesses ability to construct two dimensional designs from multicolored blocks. Administered by Outcomes Specialist. (P) (Upload: WASI-II)	**2-Factor IQ**
Brief Symptom Inventory-18 **1mo (baseline), 6mo, 12mo**	The BSI provides a valid assessment of adult psychiatric status, including the domains of depression, anxiety, and somatization. Administered by Outcomes Specialist or Research Study Staff. (P) (Upload BSI)	**GSI; subtest T-scores**
Environment and Family Function of Parent		
General Functioning Scale [66] (5') **1mo (baseline), 6mo, 12 mo**	The McFad is a subscale from McMaster Family Assessment Device (FAD).12-item scale is an overall measure of family functioning and has been shown to interact with illness severity and pediatric outcome studies using the FAD. Completed at study entry, 6mo, and 12 month evaluation to track changes in family function over time. Administered by Outcomes Specialist or Research Study Staff. (P) (Upload: Adapt McFad v1.0)	**Total score**

Note: 1mo, 6mo, and 12mo time points are approximate testing periods. Assessments will primarily be administered by Outcomes Specialist in the outpatient clinic/office or at home visits, except in some instances:

3 1) BSI and McFad questionnaires may be administered in hospital by research study staff to obtain baseline assessment while the infant and/or mom are still in hospital (may be performed by Outcomes Specialist at 1mo outpatient visit if unable to administer while in hospital).

4 2) GOSE-E Peds and BISQ will not be performed at the 1-month time point if the infant is hospitalized at timeframe of testing period; we anticipate all infants will be discharged before the 6mos assessments.

3) If study staff are unable to do assessments in person (i.e., study staff unable to schedule assessment when subject is in-patient, at outpatient clinic/office or home visit) the following questionnaires may be performed by research study staff over the phone: GOS-E-PEDI, PedsQL, PEDI, BISQ, Bayley S&E, BSI, McFad. The Bayley iii measures of neurodevelopment and WASI cannot be performed over the phone.

4) *WASI may be administered anytime throughout the study period by Outcomes Specialist.

2.3 Inclusion/Exclusion Criteria

A total of 230 full-term (≥37wks gestational age) newborn infants exposed to opioids *in utero* will be studied over the five-year funding period: 100 at UMass and 130 at UPitt.

2.3.1. Inclusion Criteria. Infant inclusion criteria include documented opioid drug exposure (i.e., positive toxicology screen; exposure questionnaire and medical record history) and comprise the general population (Worcester, MA and Pittsburgh, PA demographics) without restriction in regard to gender, race or socioeconomic status. Infants may also have additional prenatal poly-drug exposure (e.g., benzodiazepines, barbiturates, amphetamines, cannabinoids, alcohol, nicotine and/or caffeine). Inclusion of pregnant women is for the sole purpose of obtaining consent to study the infant post-delivery, and to review infant and maternal medical records. Pregnant women are included because we will be recruiting pregnant women who are at risk for delivering infants with NAS due to drug exposure in utero. Prenatal consents are needed to help expedite feasibility of study of infants soon after delivery. Infants will not be studied in utero, but will only be studied after delivery.

2.3.2. Exclusion Criteria. Subjects with clinically significant fetal anomaly, congenital abnormality, adverse pregnancy outcome, hydrocephalus or intraventricular hemorrhage >grade 2, seizure disorder not related to drug withdrawal, clinically significant cardiac shunt, anemia (hemoglobin<8g/dL), requires mechanical respiratory support or is being treated for MRSA or infection at the time of the study will be excluded, or other medical condition aside from NAS will be excluded. Informed consent will be obtained from parent(s) or legal guardian of all participants.

2.4 Sample Size and Power Calculations

For all Aims there is sufficient sample size to detect clinically meaningful differences with 90% power, described below:

2.4.1. Specific Aim 1. We use the Finnegan NAS score as the primary outcome for this aim. From Nayeri et al. [70] and our own pilot data, the Finnegan NAS score in opioid-exposed infants had a SD of 2.0-2.5. Assuming a standard t-test with a two-sided alpha level of 0.05 for the unadjusted comparison of the Finnegan scores at a particular time point with the more conservative standard deviation (SD.=2.5), the sample size of 115/group can detect a difference of 1.1 with 90% power. Taking into account the repeated measures of the Finnegan NAS score, assuming intra-infant correlations of 0.5-0.7, we will have 90% power to detect a difference of 0.80-0.95 in a mixed effects model for the overall (i.e., across time) treatment group coefficient. With a mixed effects model, we will also add covariates as described above to determine an adjusted treatment effect. We expect that this model may have even more power than described here due to the partitioning of the overall variance among the covariates. Because infants are hospitalized and under observation until release, we expect only minimal attrition and loss of information.

2.4.2. Specific Aim 2. We use Movement as primary outcome for this aim. Based on our preliminary data in 26 NAS infants (OFF: mean movement 40% of condition time, SD=10%; ON: mean movement 26% of condition time, SD=9%) and

assuming a two-sided paired t-test at alpha=0.05 for the unadjusted treatment effect, we estimate 25 infants per group will give us 90% power to detect a reduction of 7% in movement between the two treatment groups (a relative reduction of about 20% from 40% in OFF to 33% in ON) with a conservative SD of 10% (from the pilot study).

2.4.3. Specific Aim 3. We use Bayley-III as primary outcome for this aim. We anticipate an attrition rate of ~40% in the 1-year follow-up assessments. Assuming a sample size of 60 children/group at 1 year with a two-sided standard t-test at alpha=0.05 and a SD of 14 for the Bayley-III cognitive composite scale, [71] we will have 90% power to detect a difference of 8.5 (or about a 12% difference) between the two groups at 1 year of age. The other Bayley scales have similar SDs, so the results will be similar. For a longitudinal analysis of the Bayley-III cognitive composite scale over the follow-up visits (1, 3, and 12 months of age), we will use a mixed effects model as above with months of age as the time metric in the model. Assuming the same sample size with intra-child correlations of 0.5-0.7 for a mixed effects model with a two-sided test for the treatment group coefficient at alpha=0.05, we will have 90% power to detect a treatment effect of 6.8-7.4 (depending on the correlation) using the treatment group coefficient. We can also add covariates to this model to estimate an adjusted treatment effect.

Each child will be classified as impaired or not based on the results of the battery of tests given over one year.[69] Assuming a worse-case scenario (in terms of SD of a proportion) of 50% impairment in the SCC group, with 60 children/group we will have 90% power to detect an unadjusted absolute improvement of 28% (50% vs. 78%) or a relative improvement of 56% in the SVS group with a z-test with a two-sided alpha =0.05. For an adjusted estimate of the improvement in percent impairment at one year, we will use a logistic model with other covariates added. For a longitudinal assessment of impairment, we will use a GEE longitudinal logistic model with the same approach for model building as above.

5 TRIAL MANAGEMENT

3.1. List of Participating Enrolling Clinics or Data Collection Centers

1. University of Massachusetts Medical School:
    1) University of Massachusetts Memorial Hospital:
        a) Faculty and Resident Outpatient Obstetrical Clinics
        b) NICU Prenatal-NAS Clinic
        c) Newborn Nursery
        d) NICU/CCN
    2) University of Massachusetts Children's Center
        a) Pediatric Unit/Outpatient Outcomes Assessment Facilities
2. University of Pittsburgh
    1) University of Pittsburgh Medical Center and Magee Women's Hospital of UPMC:
        a) Outpatient Obstetrical Clinics
        b) Pregnancy Recovery Center

c) Newborn Nursery/Well-Baby Nursery
d) NICU
2) Mercy Hospital at UPMC
a) NICU

3.2. Projected Timetable

Benchmarks	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated Enrolled Subjects UMass/UPitt (230 total: 100UMass; 130UPitt)	25/22	25/36	25/36	25/36	
Data Safety and Monitoring Board: Bi-annual reports	X	X	X	X	X
Monthly Meetings with Research Personnel	X	X	X	X	X
Investigator Site Visits	X	X	X	X	X
Aim 1 and Aim 2: Newborn In-hospital Studies: Demographic/Medical Histories; Mattress SVS/SSC (daily); Actigraph (daily); 2 full physiology studies (10-15/yr)	X	X	X	X	X
Aim 3: Outcomes Studies Telephone Interviews; Outpatient Outcomes (3 sessions)	X	X	X	X	X
End of Year Report: Deliver up-to-date data base (demographic, medical, actigraph, outcomes testing); Deliver copy of study logs; Summary Report by site PIs	X	X	X	X	X
Investigators Present Preliminary Data at Scientific Conference/s			X	X	X
Data Collection Complete				Newborn Studies	Outcomes Testing
Final data sets delivered to UMass biostatisticians; PIs submit final site reports: study enrollment and attrition for each arm of study; Final Analysis and Writing					X

Table 3. Timeline of Benchmarks.

3.3. Target Population Distribution (e.g, Women, Minorities, etc)

The proposed study requires involvement of human subjects, specifically infants, for the purpose of investigating the therapeutic efficacy of SVS for reducing symptomatology and pathophysiological instabilities associated with neonatal abstinence and drug withdrawal, and for improving neurobehavioral outcomes. We will attempt to recruit subjects who are male or female, and from all ethnic backgrounds. We will not exclude subjects for any reason based on race, sex, religion, ethnic background or national origin. The racial mix of the Worcester, MA and Pittsburgh, PA regional areas are identified in Table 4. We expect to be able to do the same for the proposed study with the caveat that the proportions of minorities will reflect the approximate subpopulation proportions of patients admitted to UMass and UPitt with intrauterine opioid exposure.

Table 4. Demographic Characteristics of Regional Maternal Population.

Maternal Race	UMass (%)	UPitt (%)
African American	5.3	19.7
Hispanic or Latino	10.5	1.1
Asian	4.7	2.4
Caucasian	78.8	75.2
Native American	0.4	0
Two or More Races	2	1.6

4. DATA MANAGEMENT AND STATISTICAL ANALYSIS PLAN

4.1. Data Acquisition and Transmission

4.1.1. Specific Aim 1. Determine the efficacy of SVS as a non-pharmacological therapy complementary to standard clinical care (SCC) for reducing severity and duration of opioid withdrawal in newborns compared to SCC alone - Standard Measurements and Recordings.

1) Medical history. Prenatal exposure (e.g., prescribed maintenance therapy, prescription drugs and substance use during pregnancy including toxicology screens indicating drugs of exposure) and demographic data (gender, race, gestational age, birth weight, birth head circumference, delivery mode, anesthesia at delivery) will be obtained from infant and mother via questionnaire and medical records to help identify variables that may be associated with withdrawal and outcome measures. Subject's medical records will be reviewed and additional history will be obtained from parent/guardian, including review of child's mother medical records if the child was delivered at UMass. We request protected health information from general medical records and review of statutorily protected records at this institution to: 1) Obtain toxicology reports indicating drugs of exposure and other relevant records pertaining to NAS; 2) Make sure the child meets our inclusion criteria. An example would be to confirm that a child has not been diagnosed with a disorder that may cause cardio-respiratory instability, such as intraventricular-hemorrhage greater than grade 2; 3) Obtain information about factors that may affect responses we observe during stimulation. For example, pregnancy or delivery complications, exposure to drugs in utero, or prescribed medications that may alter breathing and heart rhythms. We request to review both the child's and mother's medical records for information from cardiac studies, nursing and respiratory therapy notes, clinical monitor information, discharge summaries, EEG/EMG studies, laboratory results, operative procedures, conclusive pathologies, clinical problem list, and pulmonary, radiology and rehabilitation information. There will be 1-year follow up on study infants through medical record and telephone interview. Data will be entered by a research investigator via secure password protected computer into REDCap database (REDCap Consortium, Vanderbilt University) – see **4.2 below Data Entry Methods**.

2) Chart Review/Bedside Log. NAS severity scores. The infant's clinical-care nurses at each site are routinely trained on the NAS assessment tool (modified

Finnegan Scale)[63] as part of clinical education; this helps ensure reliability of scores. Nurses score the infants' withdrawal severity ~every 3-4 hrs to assess changes in central, autonomic, vasomotor and gastrointestinal function. Daily NAS scores, weight (gain/loss; trajectory), head circumference, routine feed type (formula or breast milk), pharmacological management (medication, dose normalized for body weight), and birth date and date of hospital will be obtained from medical and/or nursing chart review. A computerized and/or paper log (de-identified, subject id only) will be kept by the infant's bedside to record when the infant is in the crib, and nursing/parent interventions (e.g., feeds, diapering, caregiver cuddling, and placement in motorized swings). This provides some indication of the infant's routine clinical care since investigators cannot be at the bedside 24/7. A separate log kept by investigators will be used to record pre-programmed time onset and offset of SVS (i.e., to verify daily automated SVS coinciding with log indicating when infant is in the crib to receive the intervention). Data will be entered by a research investigator via secure password protected computer into REDCap database.

3) <u>Movement Activity.</u> Movement periods will be assessed via actigraphy, a simple non-invasive measurement using a wireless, lightweight sensor worn around the infant's limb (Respironics®). The sensor is ~1.5"x1" and held in place with a soft foam tapeless wrap (Posey®). Actigraph sensors applied to the infant's limb will continuously record the frequency of movements throughout the duration of the infant's hospitalization, starting within 24-48 hrs post birth. This will allow measurement of frequency of leg movements (index of irritability, sleep fragmentation, wake and quiescence (index sleep) throughout hospitalization).[46, 47] Data will be recorded in 1-min epochs to evaluate for movement frequency (index of activity) and quiescence over 12h and 24h intervals and/or during periods when infants are documented in the crib (mattress on or off). Digitized signals will be stored on electronic data base. Data will be analyzed via computerized programs, stored in excel spreadsheets, and entered by a research investigator via secure password protected computer into REDCap database.

4.1.2. Specific Aim 2. Examine physiological responses to SVS compared to SCC at two stages of withdrawal severity – Standard Measurements and Recording.

Changes and relationships among physiological signals will be quantified in a sub-population of study infants at UMass. For each session, physiological signals will be recorded continuously for ~6-8 hrs using proprietary acquisition system. Respiratory inductance plethysmography will be used to measure infant's breathing (Somonstar®); infant's abdominal muscle movement will provide detection of interbreath intervals (index of respiratory stability) and respiratory rate. Electrodes over the skin surface of the chest will be used to record electrocardiographic activity (ECG; Embla®) to allow for detection of cardiac R-R intervals (index of interbeat variance and heart rate). A probe attached to the infant's foot will measure arterial-blood oxygen concentration (Masimo®). Quality of the plethysmographic activity characterized in the pulse signal will also allow for identification of movement period duration. Movement frequency will be assessed with actigraphy using a wireless sensor worn around the infant's limb (Respironics®). Infant axillary temperature will be measured continuously with a sensor placed under

the infant's armpit or back (Physitemp®). Environmental changes in sound intensity and light level will be measured with meters placed in the crib near the infant's head (Extech®). Overt behavioral data will be recorded using sound-video camera with a wide-angled lens.

Physiological data will be digitally recorded (~50-1kHz samples per channel) using an acquisition system that directly obtains signals from the NICU bedside monitor (Philips®; Wyss Institute, Harvard University) or via an independent system (Embla®). These systems enable fully synchronized recordings of physiological signals, audiometry, photometry and digital video images. Comments regarding routine nursing assessments and other relevant information (e.g. feeding, pharmacological dosing) will be typed and time stamped along with the physiological data stream. Acitgraph activity will be digitally recorded independent of the full-acquisition system. All signals, video images and germane data (e.g., medical histories of infant and mother, NAS severity assessments) will be stored on electronic data base. Investigators will also manually record relevant study information (timing and mode of experimental conditions, nursing assessments, feeds, medications etc) stored in the electronic data base.

Data is analyzed via proprietary software and via advanced computational models of analysis developed for this study. Final outputs will be stored on password protected computers in excel data bases and will be entered by a research investigator via secure password protected computer into REDCap database.

***4.1.3. Specific Aim 3*.** Compare neurobehavioral outcomes in in the first year of life between infants who received SVS and those who received SCC – Standard Measurements and Recordings.

1) <u>Follow-up Chart Review and Telephone Interview</u>. For a period of up to 14 months post hospital discharge we will review hospital medical records for inpatient and outpatient visits (if the infant is treated at UMass or UPitt) for information related to outcomes for neonatal drug exposure. We will also follow-up for 14 months post-hospital discharge with phone-call questionnaires (approx. every other month) to help identify outcomes associated with infants requiring prolonged pharmacotherapy and those discharged without medication, and to determine if there are differences in outcomes in infants treated with SVS vs SSC. Data will be entered by a research investigator via secure password protected computer into REDCap database.

2)<u>Anthropomorphic Examination</u>. Infant weight, height, and head circumference are measured in the delivery room and recorded in medical record throughout hospitalization. Data will be entered by a research investigator via secure password protected computer into REDCap database.

3) <u>Neurobehavioral Assessments</u>. Outpatient assessments will be conducted at 1 month, 6 months and 12 months (see Table 2). Data will be entered by a research investigator via secure password protected computer into REDCap database.

4.2 Data Entry Methods

The data for this study will be recorded in a REDCap database (REDCap Consortium, Vanderbilt University) in the secure regulated environment (rStats) at the University of Massachusetts Medical School. This Unix-based environment is not accessible from outside of the medical school and only medical school staff with IRB approval are assigned an account in this environment. We will program the system for a single entry with validation rules for validity, consistency, and normal range values at the time of entry and comprehensive edits through multivariable edit approaches conducted after the data have been submitted to the main data base. Edit queries will be resolved by clinic staff with corrections posted to the database through the REDCap system, which enforces an audit trail for all changes.

The main study database will be stored on a secure server in the University of Massachusetts HIPAA-compliant data center with daily back-up. REDCap will be used within the rStats environment to protect any PHI/PII data that are collected as part of the study. We will strive to minimize collection of such data and REDCap will be programmed to segregate that data from the main study data so that exports for analysis will be deidentified.

Data will be exported from REDCap for import into the latest version of statistical software (e.g., SAS, SAS Institute, Cary, NC) for all analysis. All reports and analyses will be generated from these files using the latest version of SAS (currently SAS 9.3). Data files (and accompanying SAS programs) that are used for reports, presentations, or publication will be archived as required past the end of the study. The REDCap system will be programmed and maintained by study staff at the U Mass Medical School while data entry will be performed by research study staff at the U Mass Medical School and at the U Pittsburgh Medical School.

To the extent possible, data from the laboratory assays will be conveyed electronically and uploaded directly into REDCap. Edit checks will be built into the upload process to identify any out-of-normal range values. Any edit queries will be forwarded to the appropriate laboratory for resolution. If a direct upload is not possible, a REDCap data entry screen will be implemented for the laboratory data.

4.3. Data Analysis Plan

***4.3.1. Overview*.** Table 1 provides a summary list of outcome variables for each Specific Aim. Descriptive statistics will be calculated (means/SD or median/IQR) by treatment group. Because infants will be repeatedly observed and measured, initial analyses comparing outcomes between the treatment groups (SVS vs SCC) will be conducted using standard approaches assuming a normal distribution (i.e., two-sample t-test) or using non-parametric alternatives if assumption of a normal distribution is not appropriate (i.e., Mann-Whitney U Test). We will use mixed effect models to analyze the repeated measures over time. These models will estimate the trajectory of outcomes over time within each treatment group as affected by condition and other factors of interest. The time metric for these models will be hrs since birth for Aims 1 and 2 for each measurement so that the trajectories will relate to the same baseline

measurement for all infants. Treatment group will be considered as fixed effect in the models, with other factors considered to be either fixed or random effects, depending on the nature of the factor: opioid only vs opioid+other; gender, delivery mode (vaginal or caesarean-section); delivery anesthetics (none vs anesthetics). Comprehensive histories from medical record and questionnaire will allow us to examine the influence of additional variables

***4.3.2 Specific Aim 1*:** We will use mixed effects models as described above to examine whether infants treated with SVS compared to SCC have: 1) Lower daily average and maximum NAS scores; 2) Less morphine requirement (primary pharmacological treatment for managing NAS at both sites; cumulative dose normalized for body weight); 3) Enhanced velocity of weight gain throughout hospitalization; and 4) Shorter hospitalization length of stay. A model will be fit for each outcome using Nagelkerke's R^2 to determine the model with the best fit using the ratio of the -2 log likelihoods for the model with covariates compared to the intercept-only model. Factors of interest will be included in the model as appropriate and interactions with treatment group will be tested as well. The interactions will indicate whether the treatment effect is the same across subgroups. Additional analyses to identify groups of infants who do particularly well (or poorly) with SVS will be conducted using latent class techniques, such as cluster analysis (for continuous variables) or latent class analysis (for discrete variables). The factors of interest will include: drug exposure (e.g., prescribed maintenance therapy, prescription drugs and illicit substance; with or without poly-drug use), demographic data (gender, race, gestational age, birth weight, birth head circumference, delivery mode, anesthesia at delivery), and feed type (formula or breast milk).

Movement: Actigraphy (movement activity frequency) will be compared across days and between Groups using similar mixed effects models as above. The outcomes of interest are actigraphy throughout hospitalization to determine if SVS reduces movement and increases quiescence episodes over time (12 and 24 hour assessments) compared to SCC.

***4.3.3. Specific Aim 2*:** Study design allows systematic quantification of condition effects on breathing (IBI variance and respiratory rate), cardiac rhythm (R-R variance and heart rate), movement activity (frequency and duration), blood oxygenation (durations<85%), and skin temperature. Histogram of frequency-bands of cardio, respiratory and movement incidents will be determined. As with Aim 1, mixed effects models will be used to examine if SVS, within infants and between SVS and SCC infants: 1) Decreases irritability and sleep disruption/fragmentation indexed by movement frequency and duration; 2) Improves cardio-respiratory control: reduces bradycardia/bradypnea, tachycardia/tachypnea and increases incidents of eucardia/eupnea; and 3) Reduces other NAS symptoms: e.g., temperature; oxygenation. **Additional computational signal analysis.** We have developed novel statistical point process algorithms that measure cardio-respiratory dynamics and movement over continuous time domains.[67, 68]The variable characteristics of respiratory (IBI) and cardiac (RR) signals are integrated with the dynamic characteristics of these signals to provide instantaneous, moving estimate of mean, variance and other

dynamic measures (e.g., spectrum, poles, frequency).[68] These measures will be used to examine temporal dynamics of respiratory and heart rate rhythm, and explore corresponding physiological relationships with movement over time; e.g., Do IBI changes that reflect caudal brainstem function precede cortical behaviors such as arousal (e.g., movement)? Time series of movement periods will be analyzed using Wavelet derived SAP throughout stimulation ON and OFF to evaluate temporal dynamics including: 1) Response time for improvement in rhythm relative to the onset of stimulation; 2) Whether there is loss of efficacy over time (during each 30 min stimulus period as well as from one period to the next); 3) Whether improvement in rhythm persists following offset of stimulation.

4.3.4. Specific Aim 3. One-Year Outcomes' Assessment. We will use a general linear model approach to analyze outcomes over one year, using the same model building strategies described above. Some outcomes, such as the Bayley-III scales, are collected at multiple follow-up visits so we will use mixed effects models to estimate treatment effect over time and to adjust for other covariates. Impairment is determined based on a fairly extensive neurobehavioral test battery but the component test scores are highly correlated. To control for error that results from this correlation, we will reduce the number of tests by evaluating the domain or summary scores from the various instruments and use the approach of Ingraham and Aiken[69] to determine how many deviant scores are required to identify a child as impaired. This approach calculates the criteria for abnormality when employing batteries of multiple tests by generating probability curves for exceeding cut-off criteria by chance given certain criteria (e.g., an expectation that one group will show a decrement). This type of analysis will allow us to look at rate of impairment in young children with opioid exposure and assess whether SVS compared to SSC reduces likelihood of impairment.

5 QUALITY ASSURANCE

5.1. Procedures in Place to Ensure the Validity and Integrity of the Data

Quality Assurance of data entry and data management consists of a set of proactive tools that are implemented to increase the quality of the data processing components including: (1) Form design to avoid structural missingness, orphan questions, and as many "write-in" responses as possible; (2) Training of the data entry operators on the study forms so that they are familiar with the required responses; (3) Design of the data entry screens to look as much like the paper forms as possible; (4) Specifications of the data fields to reflect the nature of the data to be entered; (5) Specification of the edit parameters and checking algorithms so that every field is verified as completely as possible; and (6) Validation of the database system to certify that data entered into the data entry screens are accurately recorded in the databases.

In other areas, quality assurance will be implemented in a variety of ways: (1) Training of the research staff on data collection techniques with periodic retraining; and (2) Immediate review of data collection to be sure that data collection forms are fully complete. All staff will be trained on the protocol and issued certification numbers for the study. Staff will have to be certified in an area (such as data entry and patient

randomization) before the study systems will allow them to perform those tasks. All study systems will require a dual level login procedure for each task.

5.2. Procedures to Guarantee the Accuracy and Completeness of the Data, During Data Collection, Entry, Transmission, and Analysis

For quality control measures, regular analyses will report on: (1) Number of missing data items; (2) Number and type of forms that are failing edit; and (3) Distribution of data to look for outliers. A Quality Control report will be generated at the same time as the DSMB report for review by study leadership and by the DSMB. In addition to the quality assurance/quality control plans for data entry described above, we will select a 10% sample of patients each quarter to review select (high-risk) data for verification against source documents, including patient characteristics and laboratory assay results. Any item discrepancies of greater than 2% will be discussed with the site data coordinator and retraining/additional observation instituted if required.

Only research team members will have access to subject identifying information, which will be stored electronically only in the participant tracking database in the U Mass Medical School regulated environment. Each patient will be identified with a study ID number which will be used on all data collection forms. Only the participant tracking database will have the link between the study ID number and the PII of the patient.

5.3 Monitoring Missing Data

Reports on missing data will be reviewed by the DSMB, including missing forms and missing data items. In addition, for data that are missing, we will consider appropriate imputation procedures, such as model-based multiple imputation, for study analyses. To identify spurious data, we will implement edit checks at data entry for values that are out of normal range, inconsistent values, and improper data entry so that most problems will be detected during data entry. Additional edit checks will be implemented to run when the data are submitted to the main study database. These will include edits across visits and across forms, so that large changes between visits and inconsistent responses between case report forms will generate an edit query. Edit queries will be forwarded to the appropriate clinical site coordinator for resolution through changes done through REDCap. The implementation of REDCap at University of Massachusetts Medical School has the audit trail fully implemented so that any changes to the original submitted data are recorded and documented.

6 REGULATORY ISSUES

6.1. Reporting of Serious Adverse Events (SAE) and Suspected Adverse Reactions (SAR)

With regard to serious adverse events and suspected adverse reactions, both expected and unexpected and regardless of whether the SAE/SARs are considered related to the study intervention and/or the *in utero* drug exposure and subsequent NAS, they will be followed in a rigorous review process through the entire trial period. Clinical performance sites will be instructed to report all fatal events, unanticipated problems and other serious adverse events and suspected adverse reactions to the DSMB and

IRB by secure email within 24 hours of first knowledge of the event. All SAES must be reported to NIDA within 72 hours. Additionally, all current study data for that particular subject will be entered to allow for timely review by the External Medical Safety Monitor (EMSM).

The EMSM will closely monitor the incidence rates of all adverse events reported, whether serious or not, throughout the study, and will alert the DSMB if a trend is observed. A significant increase in the rate of adverse events in the SVS treatment group would be cause for concern for the safety of participants in the study. Information on adverse events will be presented in several ways: (1) Listings of serious adverse events with accompanying narrative summary by the Safety Officer with input from the Study PI; (2) Summaries of adverse events by body system and type of event. This information will be presented by blinded treatment group (i.e., SVS and SCC) to the DSMB for each group. In addition, the Safety Officer will be given treatment information in a blinded fashion, although he/she can request to be unblinded in cases where that knowledge could be critical.

Serious adverse events should not be reported for hospitalization or prolonged hospitalization in the following scenarios: for a diagnostic or elective surgical procedure related to a preexisting condition; to allow for an efficacy measure for the study; or, for a planned surgical procedure that was not the result of a condition worsening due to participation in the study.

A summary of all AEs and SAEs, a summary of all reports, and a coded list of all subjects who were terminated from the study due to study-related adverse events, will be included in reports submitted by the DSMB to the IRBs. An annual report will be submitted to the IRBs at all participating sites. NIH NIDA will also receive all reports.

6.1.1. Definitions.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.102
The clinical site investigator, on the basis of his or her clinical judgment and the following definitions, determines the relationship of the adverse event to the protocol intervention as one of the following:

- Definitely: Any adverse reaction and those adverse events that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive, e.g., improvement coinciding with discontinuation and recurrence on reinstitution.
- Probably: An AE that might be due to the use of the study intervention. The relationship in time is suggestive, e.g., improvement coinciding with discontinuation. An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s); and, other causes have been eliminated or are unlikely.
- Possibly: An AE that might be due to the use of the study intervention. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable.

6.1.2. Adverse Event Follow-Up. Subjects with adverse events (both serious and non-serious) will be followed as clinically indicated and no less often than specified by this protocol for standard follow-up of subjects enrolled in the study. At those visits, updated information on the adverse event will be collected and entered into the REDCap data capture system until the adverse event is completely resolved.

6.2 Reporting of IRB Actions to NIDA

All actions of the UMMS or U Pitt IRBs related to the conduct of this study will be reported to the NIDA Project Officer immediately. Any additional follow-up will be discussed at that time.

6.3 Reporting of Changes or Amendments to the Protocol

This study will be conducted in compliance with the protocol approved by the Institutional Review Board and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible. Any change or amendment to the protocol must have prior approval from NIDA PO.

6.4 Trial Stopping Rules

There will be no formal statistical stopping boundaries proposed for this study, although the DSMB can request such boundaries be determined at any time during the study for both safety and efficacy (including futility). However, an apparent, consistent and persistent evidence of net harm that tends to overwhelm any benefit may allow for premature termination of the study. Continuing enrollment into each cohort will be determined in an ongoing basis and at periodic intervals. The DSMB will receive a report on all reported AEs and SAEs as well as the proportion of subjects with any specific event of interest. The finding of any unexpected serious adverse event considered to be related to study intervention in 2 of 6 patients will lead to review and suspension of recruitment and review of the complete data by the External Medical Safety Monitor (EMSM).

Following the EMSM's review, the safety report (and any comments from the EMSM) will be sent to the DSMB. The DSMB will make the final recommendation for early termination versus continuation of the study after reviewing the available data. The decision will be guided by safety. In addition to the planned evaluations, the EMSM and DSMB will receive quarterly safety summary reports of enrollment, baseline demographics, withdrawals from treatment and all AEs and SAEs with information on relation to study treatment.

6.5 Disclosure of any conflict of interest (COI) in the DSMP

Conflict of Interest. The PI (Salisbury) is a co-inventor on a patent for use of the uniquely constructed mattress that delivers the SVS. There is an approved mitigation plan in place at UMass due to a potential financial conflict of interest: 1) Dr. Salisbury will not be involved in enrolling or consenting clinical study participants; 2) The consent will convey potential financial interest in the clinical study; 3) Data analysis will be subject to a biannual Quality Assurance review by a suitable member of the UMMS human research protection program not otherwise associated with the Clinical Study. We will obtain required approvals for Dr. Salisbury to conduct studies at UPitt as per the Conflict of Interest Committee requirements at UPitt.

7 TRIAL SAFETY

7.1 Potential Risks and Benefits for Participants

7.1.1. Potential Risks

There are no known risks of SVS mattress to be used in this study. While it may be difficult to discern whether changes in withdrawal symptoms are due to the intervention or to related system dysregulation of NAS, the protocol may be discontinued at any time if the investigators or the infant's doctor suspects there are any adverse effects on breathing, heart rate, temperature, oxygenation, movement-irritability or any other function.

The additional physiological recording measures to be used in this study are standard devices used on infants (e.g., surface sensors to record muscle activity, heart leads, respiratory plethysmograph belts placed around the surface of the infant's rib cage and abdomen to record movement of respiratory muscles etc); they pose minimal risk of skin irritation from the adhesive/foam bracelets used to hold the sensors in place. Potential risk of infection is minimized by using primarily disposable sensors, and cleaning with sterilizing wipes any non-disposable sensors before and after each use. There is the potential risk of breach of confidentiality, but this is minimized by using alpha-numeric study code to identify subject data; furthermore all research related computers username and password protected. Names will not be used in any reports or publications of this study.

7.1.2. Potential Benefits

There are no known immediate direct benefits to the subjects or others. Although it is hoped that infants assigned to the SVS group may benefit from SVS if NAS symptoms are reduced and 1-year outcomes are improved, this will not be evident until completion of the study.

7.2 Collection and Reporting of AEs and SAEs

Adverse events, as defined in the protocol, will be collected from the date and time of randomization to the date and time of hospital discharge as discussed above in

Section 6.1. All adverse events will be coded using MedDRA and will be reported to the DSMB in tabular form organized by patient, showing the adverse event with the preferred term grouped within system organ class as well as relatedness to the treatment. Tables will show the treatment-emergent adverse events, i.e., adverse events that occurred after randomization or worsened after randomization. These tables will be reviewed at every DSMB meeting (and more frequently if requested).

7.3 Management of SAEs or Other Study Risks

In the event of a serious adverse event, from disease or drug, the clinical presentation will be immediately reviewed by the study leadership. Management of the SAE will be chosen on the basis of the collective clinical decision-making of the investigators and the other physicians involved in the patient's care.

Any fatal events, unanticipated problems and other serious adverse events and suspected adverse reactions will be reported to the DSMB and IRBs by secure email **within 24 hours of first knowledge of the event**. Additionally, all current study data for that particular subject will be entered to allow for timely review by the External Safety Monitor.

SAEs will be reported to the DSMB and IRBs as indicated above. The DSMB also will review tabulated summaries of SAE in the same format as AEs as well as listings of the details for each SAE, grouped within infants (for those infants with more than one). A narrative summary of the SAE and treatment for it will be included.

An annual report will be submitted to the IRBs at all participating sites. A summary of all adverse events (AEs) and serious adverse events (SAEs), a summary of all reports, and a coded list of all subjects who were terminated from the study due to study-related adverse events, will be included in reports submitted by the DMSB to the IRBs. The funding institute, NIH OBA and FDA will also receive all reports.