Study design and rationale for a randomized controlled trial to assess effectiveness of stochastic vibrotactile mattress stimulation versus standard non-oscillating crib mattress for treating hospitalized opioid-exposed newborns

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ABSTRACT

The incidence of Neonatal Abstinence Syndrome (NAS) continues to rise and there remains a critical need to develop non-pharmacological interventions for managing opioid withdrawal in newborns. Objective physiologic markers of opioid withdrawal in the newborn remain elusive. Optimal treatment strategies for improving short-term clinical outcomes and promoting healthy neurobehavioral development have yet to be defined. This dual-site randomized controlled trial (NCT02801331) is designed to evaluate the therapeutic efficacy of stochastic vibrotactile stimulation (SVS) for reducing withdrawal symptoms, pharmacological treatment, and length of hospitalization, and for improving developmental outcomes in opioid-exposed neonates. Hospitalized newborns (n = 230) receiving standard clinical care for prenatal opioid exposure will be randomly assigned within 48-hours of birth to a crib with either: 1) Intervention (SVS) mattress: specially-constructed SVS crib mattress that delivers gentle vibrations (30–60 Hz, ~12 μm RMS surface displacement) at 3-hr intervals; or 2) Control mattress (treatment as usual; TAU): non-oscillating hospital-crib mattress. Infants will be studied throughout their hospitalization and post discharge to 14-months of age. The study will compare clinical measures (i.e., withdrawal scores, cumulative dose and duration of medications, velocity of weight gain) and characteristic progression of physiologic activity (i.e., limb movement, cardio-respiratory, temperature, blood-oxygenation) throughout hospitalization between opioid-exposed infants who receive SVS and those who receive TAU. Developmental outcomes (i.e., physical, social, emotional and cognitive) within the first year of life will be evaluated between the two study groups. Findings from this randomized controlled trial will determine whether SVS reduces in-hospital severity of NAS, improves physiologic function, and promotes healthy development.

1. Introduction

Opioid-use during pregnancy and post-natal effects on the neonate continues to be a growing and costly public health problem [1–5]. Particularly alarming is the high rate of use and misuse of prescription opioids, with reports of use of these extremely addictive narcotic pain

medications during pregnancy ranging between 5% and 42% [4,6]. Latest reports show that on average 8 of every 1000 hospital-born newborns nationwide are diagnosed with withdrawal from opioid exposure *in utero*, which translates to approximately 4 infants per hour [5]. In the United States, annual hospitalization costs to treat opioid-exposed newborns are estimated at over half a billion dollars and this does not include care after discharge [3]. Infants exposed to opioids prenatally develop physical tolerance and dependence through placental transfer [7,8]. The abrupt cessation of such substances that occurs at birth when the infant's blood supply becomes independent of their mother's results in a wide range of withdrawal symptoms and dysregulated behaviors that vary in severity from minimal to life threatening, commonly referred to as Neonatal Abstinence Syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome [8–11].

Clinically significant neurobehavioral symptoms of NAS include pathophysiologic cardio-respiratory instabilities, gastrointestinal dysfunction, and hyperirritability [9,12,13]. Despite first-line non-pharmacological management strategies to help reduce withdrawal (e. g., breastfeeding, skin to skin, swaddling, and rooming-in) [14–16], many opioid-exposed newborns require prolonged hospitalization to treat withdrawal with federally-controlled opioid agonists (e.g., morphine, methadone, buprenorphine) [10,17–20] and other prescribed medications (phenobarbital, clonidine) [18,21]. Animal and human studies suggest pharmacological interventions used to treat withdrawal may have independent, additive, or synergistic detrimental consequences on development such as impaired motor activity, altered nociceptive responses to pain including hyperalgesia, and may contribute to cognitive deficits and behavioral problems [22–26]. Treatment protocols for NAS that incorporate non-pharmacological strategies remain largely unexplored [15,27–29]. Non-pharmacologic, complementary therapeutic strategies are needed to reduce symptoms and severity of withdrawal, facilitate weaning, and reduce cumulative and prolonged exposure to pharmacologic agents, particularly among infants for whom first-line supportive care [14,15] is insufficient or not feasible.

Stochastic resonance-based techniques have been used to promote stability in destabilized biological systems – by introducing artificial noise in the form of low-level, stochastic (i.e., random, noisy) stimulation a destabilized sensory system can be converted to normal rhythms [30,31]. In a single-session study, stochastic vibrotactile stimulation (SVS) delivered through a specially-constructed crib mattress [32] improved cardio-respiratory rhythms and reduced irritability in a small cohort of full-term infants with NAS [29]. The primary aim of the current trial is designed to test mattress SVS as a therapeutic strategy for regulating destabilized systems in opioid-exposed newborns. This study will assess effects of SVS mattress stimulation throughout infant hospitalization on short-term clinical outcomes and post-discharge re-hospitalization, morbidities, and neurobehavioral development [15,33].

Despite the growing problem of neonatal opioid exposure, objective physiologic markers of withdrawal in the newborn remain elusive. A second interdependent aim of this study is to assess pathophysiologic instabilities of withdrawal using quantifiable autonomic signals (e.g., cardiac, respiratory, temperature) and assess the effects of SVS on these physiologic measures. Movement activity, an index of irritability, will also be quantified throughout infant's hospitalization using acitgraphy [34]. These objective measurements will provide insight into the progression of physiologic withdrawal in hospitalized opioid-exposed newborns and provide quantifiable physiologic effects of the SVS intervention.

In this randomized, controlled clinical trial, *Efficacy and Outcomes of a Non-Pharmacological Intervention for Neonatal Abstinence Syndrome* (NCT02801331), we will study SVS complementary to standard of care for treating hospitalized opioid-exposed newborns. Using specially-constructed crib mattresses [32] we will determine if SVS reduces symptoms and duration of withdrawal, improves autonomic function, and enriches long term developmental outcomes in full-term, intra-uterine opioid-exposed newborns compared to those receiving standard of care with hospital-issued, non-oscillating crib mattresses. This dual-site study funded by National Institute on Drug Abuse (R01DA042074; Bloch-Salisbury) is being conducted at UMass Memorial Healthcare (UMass, Worcester, MA; coordinating and primary site; Principal Investigator Bloch-Salisbury) and at the University of Pittsburgh (UPitt; Pittsburgh, PA; consortium site, Principal Investigators Bogen and Beers).

2. Materials and methods

2.1. Objectives

The objective of this trial is to assess efficacy and outcomes of SVS delivered through a crib mattress as a complementary therapeutic intervention for NAS. The study will compare clinical characteristics, progression of physiologic withdrawal, and developmental outcomes among opioid-exposed newborns receiving treatment as usual (TAU) and those receiving TAU plus a novel SVS-mattress intervention aimed at reducing NAS course and impairments. Short-term clinical outcomes, withdrawal symptomatology, and physiologic responses will be assessed throughout infants' hospitalization. Longitudinal assessments post-discharge will test whether SVS-mattress intervention improves infant physical, social, emotional and cognitive development in the first year of life.

2.1.1. Hypothesis

The primary hypothesis of this study is that complementary SVS-mattress intervention throughout neonatal hospitalization provides somatosensory perturbations that improve central and autonomic control, indexed by reductions in pathophysiologic instabilities and better short-term clinical and longitudinal developmental outcomes, compared to TAU alone. To test this, we will quantify and compare the following between infants receiving daily intervals of SVS-mattress intervention and infants receiving only TAU:

1) Clinical variables throughout hospitalization will include range and trajectory of withdrawal severity scores (Finnegan [27,35]), medication to treat withdrawal (duration; cumulative dose), velocity of weight gain, and hospital length of stay. Movement activity measured with actigraphy will be used to index irritability throughout hospitalization. Full-physiologic assessments of withdrawal, including cardiac and respiratory activity, movement activity, blood-oxygenation and thermoregulation, will be studied in a sub-cohort of infants receiving pharmacologic management in the neonatal intensive care unit (NICU) on two single-session study days; and
2) Post hospital discharge, infant developmental outcomes will be assessed up to 14-months of age, controlling for general environmental and family function, and maternal cognitive ability. Trained study staff will obtain bi-monthly developmental report from the infant's caregiver and will conduct validated, comprehensive developmental assessments with the infant at 6 mos and 12 mos.

2.2. Trial design

This study is a prospective dual site, randomized controlled parallel-group trial with two arms: (1) Intervention (SVS); SVS mattress; (2) Control (TAU); hospital-issued non-oscillating mattress. Masking of bedside caregivers (family and medical) and research staff from condition assignment is not feasible due to the vibrating-mattress apparatus (Fig. 1) and physical output of the stimulation. Outcomes personnel who conduct the follow-up assessments will be masked to subject's randomized-condition assignment.

SVS Mattress

- Contains a mechanical actuator that vibrates a soundboard embedded in the foam
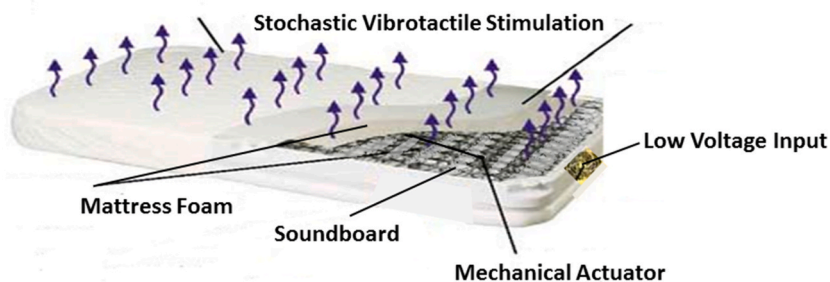- Driven by a low voltage electric current from stimulus controller

Fig. 1. Stochastic vibrotactile stimulation (SVS) mattress device.

2.3. Study participants and setting and participants

A total of 230 infant-mother dyads will be recruited over a 4-year period with follow-up assessments extending through a 5th year of the project. In-hospital bedside studies will be conducted at UMass Memorial Healthcare (UMMHC) Memorial Campus, Worcester MA (UMass site) in the NICU (including Continuing Care Nursery) and Newborn Nursery (NN), and at the consortium site (UPitt) at UPMC Magee-Women's Hospital, Pittsburgh PA, in the NICU and NN Mother-Baby and Parent Partnership Units, where subjects receive round-the-clock medical care. In-person follow-up assessments will be conducted at UMass study-staff office and UPitt outpatient-research clinic. Outcomes assessments may also be performed at the subject's home for participants with transportation limitations.

Written informed consent will be obtained from the biological mother of each infant either prenatally or within 48 h after delivery for their and their infant's participation in the study. In instances where infants are placed in state custody by the Department of Children and Families (MA) or Children, Youth and Family Services (PA) and the biological mother retains parental rights to continue participation in the study, the state-assigned caregivers may also be enrolled to participate in the infant follow-up assessments in accordance with respective state and Institutional policies. Infants for whom parental rights have been terminated by the courts after study enrollment will be withdrawn from study upon notification of termination.

The study was approved by the UMass Medical School Institutional Review Board (IRB), which serves as the IRB of record through a reliance agreement with UPitt. A NIH Certificate of Confidentiality was obtained for this study to protect subjects from disclosures and ensure confidentiality of information. We obtained a Prisoner Certification to allow biological mothers who meet the regulatory definition of prisoner but are not detained in a penal institution to participate in the study. Study enrollment started March 2017. Data collection is expected to be completed by the end of 2021.

2.4. Eligibility and Exclusion Criteria

Eligibility Criteria: Eligible participants are full-term, newborn infants (≥37 weeks gestational age) at risk for NAS due to opioid exposure *in utero* and receiving care in the NICU or NN at UMass or at UPitt. At-risk is defined as infants who present with confirmed meconium and/or urine toxicology report and/or documented medical record for one or more *in-utero* opioid exposures (e.g., methadone, buprenorphine, oxycodone, heroin). Infants may have additional prenatal exposure to other drugs (legal or illicit use, including but not limited to benzodiazepines, barbiturates, amphetamines, cannabinoids, cocaine, alcohol, nicotine).

Exclusion Criteria: Infants are excluded from study participation if born less than <37 weeks or having any of the following medical conditions: one or more clinically significant congenital anomalies, hyodrocephalus, intracranial hemorrhage > grade 2, neonatal seizures not related to drug withdrawal, anemia with hgB<8.0 g/dl, hypoxic-ischemia encephalopathy, respiratory failure requiring invasive ventilatory support, or receiving treatment for bacterial or other viral conditions. Infants can also be excluded if not approved for study by their attending physician.

2.5. Study device: mattress stochastic vibrotactile stimulation (SVS)

The SVS mattresses employed in this study are experimental devices (non-commercially available), not approved by the U.S. Food and Drug Administration as a treatment for NAS. The mattresses were constructed by engineers at the Wyss Institute at Harvard University and Cofab Design, LLC using patent specifications [32]. Device components may be modified during the study trial with improved technologies that provide equivalent mattress output to help ensure consistency of mattress integrity. Each trial mattress was individually constructed with the same dimensions (23″x12″x3″) to fit into the standard hospital crib (26″x14″x8″) and to provide whole-body SVS (30–60 Hz, ~12 μm RMS centrally maximized with near-linear surface displacement; Wyss Institute, Harvard University; Cofab Design, LLC [32]). They were designed so that the foam vibrates throughout the entire mattress (as depicted in Fig. 1) to gently stimulate the infant, analogous to prototype mattresses

used in other short-term studies [1,29]. The UMMHC Biomedical Engineering and the UPMC Magee-Womens Hospital Clinical Engineering departments will provide annual certification of the electrical safety of the mattress devices. Engineers at UPitt, Wyss Institute, and Cofab Dsign, LLC will routinely test and calibrate mattresses to ensure integrity is maintained throughout the project period.

2.6. Procedures

Fig. 2 provides a schematic of the target enrollments and subject participation in the study interventions and assessments for each site over the 5-year period. We created a study *manual of operations* that research staff are trained to follow to ensure both sites follow the same code of conduct, which details all areas of the study project described below. The lead principal investigator (PI; EBS) will travel between sites to initially assist with setting up infrastructure and training of study staff and thereafter to help ensure consistency in protocol administration and data collection, and device integrity. Throughout the trial, research staff will participate in routine dual-site conference calls to review procedural issues, progress and problems, and to promote ongoing collaboration with the interdisciplinary team of investigators.

2.6.1. Recruitment

Infants at risk for NAS due opioid exposure *in utero* will be pre-screened for eligibility using a HIPAA waiver through electronic medical records (EMR) or may be identified to investigators by medical care-givers. Infants will be recruited either prenatally in the obstetrical clinics and prenatal clinics for pregnant women with opioid-use disorder, or post-delivery in NICU, NN and Mother-Baby Units. Upon permission from an attending or primary medical-caregiver responsible for the infant's care, the biological mother will be approached for informed consent by a research investigator with consenting privileges and in accordance with IRB and respective state regulations.

2.6.2. Randomization

Infants will be randomized and assigned to either (1) Intervention group (SVS) or (2) Control group (TAU). Randomization is performed by assigned research personnel through an automated, audited-password protected program developed and administered by the Department of Population and Quantitative Health Science at UMass. The program was designed separately for the UMass and UPitt sites. Male and female subjects will be separately randomized using a modified force-block design allocating a maximum of 6 assignments for a given period (i.e.,

up to 3 SVS assignments and 3 TAU assignments) to help ensure even allocation of the intervention for each site and within each gender. Given the unknown and varying length of stay for each participant, the intervention assignment is returned to the randomization pool upon the infant's hospital discharge to maximize assignment of eligible candidates. Only 3 SVS mattresses and 3 TAU assignments will be allocated for randomization; additional mattresses are available to replace mattresses should they become inoperable within a study period or fail integrity-calibration tests. No more than 6 infants will be enrolled in each hospital site at a given time; recruitment will be paused should this limit be reached and resume upon infant discharge from hospital, opening a SVS or TAU assignment.

(1) SVS. For infants assigned to the SVS mattress, the hospital crib mattress will be replaced with the specially constructed mattress to provide gentle vibrations during mattress stimulation periods (Fig. 1). Infants will receive daily interventions of continuous intervals of SVS throughout hospitalization while in the crib. The device is designed to automatically cycle on and off at 3-hour intervals. Infants are not always in their crib (e.g., held by care-giver, feeding, bathing, placed in other hospital-issued infant seats – all part of the standard of care) and it is not feasible to provide round-the-clock research staffing to monitor when the infant is in or out of their crib. 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 at both sites. The mattress stimulation will cycle on and off even if the infant is not in his/her crib. An uninterrupted battery supply will be placed on a crib shelf or rolling-cart alongside the crib to help ensure continuous duty cycle when infants are moved in the units, such as between nursery and maternal rooms. The start and stop times of the mattress cycle will vary among subjects as a function of initial enrollment time. The mattress duty-cycle times, including initial start and any subsequent stop/restart times, and routine calibration of mattress integrity will be documented in the study data base.

(2) TAU. Infants randomized to this arm will be assigned to the standard, non-oscillating hospital crib mattress throughout hospitalization and will not receive any periods with the mattress SVS.

2.6.3. Infant daily assessments throughout hospitalization

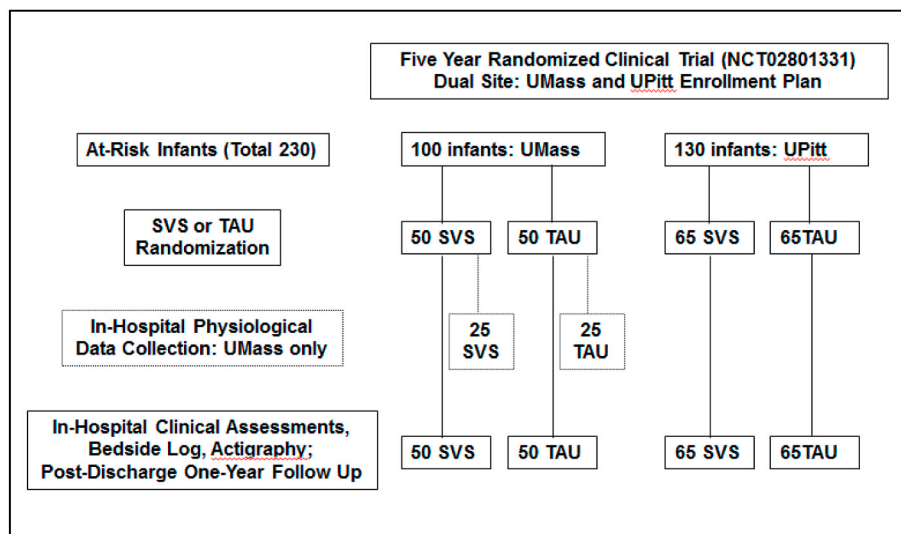Infants will be enrolled within 48-hours post birth. Infants at both

Fig. 2. Target enrollment plan. SVS=Stochastic vibrotactile stimulation mattress (intervention); TAU = Treatment as usual (control).

sites are typically observed clinically for signs and symptoms of withdrawal [27,35] in the NN/Mother-Baby Units for 4–7 days. Infants who warrant pharmacologic treatment for severity of withdrawal based on common conventional clinical protocol [36] are transferred to the NICU. Regardless of randomization assignment, all infants will receive respective site standard of care (e.g., unit assignments, clinically-determined pharmacotherapy). Caregivers (medical and family) will be instructed to care for the infant-subject as they typically would do, including feeding, holding, unit volunteer trained Cuddlers, or placing the infant in hospital-issued motorized seats, independent of assignment.

To help ensure safety of infants assigned to the SVS mattress intervention, if the infant does not show significant signs of withdrawal during the first few days of life (i.e., not transferred to NICU for pharmacotherapy), the mattress intervention will be turned off 12–24 h before anticipated discharge from NN to home to allow medical caregivers to observe the infant without the stimulation prior to hospital discharge. Should the infant exhibit signs of withdrawal that the medical team determines warrants medication to treat, the infant will be transferred to the NICU as per standard of care and the SVS will resume as per study protocol, cycling every 3 h until the infant's medication is stopped. At both sites, this is typically about 24–48 h before the infant is discharged to home.

For all infant participants, research staff will record routine cares and daily clinical assessments obtained from EMR into the study data base, including feed type, route and amount (i.e., breastmilk or formula, breast fed or bottle and duration and volume respectively), and infant weight. Standard clinical-care withdrawal scores [27,35] and pharmacological treatment will be recorded throughout the course of the infant's hospitalization and factored into the analyses.

In addition to assessing standard clinical measures of withdrawal throughout hospitalization, this study will use actigraphy as a novel approach to obtain an objective assessment of infant "irritability." Actigraphy is a simple, non-invasive tool that measures movement activity. Only a few, small studies have used it to assess severity of neonatal withdrawal (e.g., Ref. [34]) including a pilot study by our group [37].To provide a quantifiable measure of irritability, a small, lightweight actigraphy sensor (Philips Actiwatch 2, Respironics, Murraysville, PA) will be worn around the infant's lower leg using a soft, foam band throughout hospitalization. The location of the sensor on the leg will be alternated to protect against skin irritation. The actigraphy data will be routinely downloaded into the study data base. Movement activity will be assessed during periods when the infant is in the crib when the mattress is vibrating (SVS ON) and when the mattress is OFF (SVS OFF), allowing for comparisons between periods of SVS ON and SVS OFF with infants assigned to the SVS mattress and with infants assigned to TAU (i.e., SVS OFF).

Caregivers (i.e., family and medical) will be instructed to use a computerized study log at the infant's bedside to record infant's daily bedside activities, including time the infant is in the crib, being held or fed, in hospital-issued motorized seats (standard of care), and routine nursing cares. Fig. 3 illustrates bedside set-up, including the bedside computerized log and mattress setup.

2.6.4. Infant single-session physiologic assessments in-hospital

To further explore objective indices of withdrawal, a subset of infants at the UMass site who receive pharmacotherapy for withdrawal may participate in 1–2 full-physiology recording sessions during their hospitalization in the NICU. These sessions will last approximately 8–12 h, conducted approximately between 6am and 6pm. To better understand the physiology of withdrawal in newborns, controlling for time from birth, subjects will be studied between 5 and 7 days old, and between 12 and 14 days old. Infants will be studied in their unit bedside crib in accordance with their original study randomization assignment (SVS, using the infant's same 3-hour ON/OFF duty cycle on the study day; or TAU, no stimulation). During these sessions, additional sensors will be applied to the infant analogous to our previous studies [29,38]. Continuous cardiac, respiratory, blood-oxygenation, axillary temperature and movement activity (duration and frequency) will be recorded throughout the session day to quantify physiologic markers of opioid withdrawal among infants at the same age of life. Physiology will be compared between periods of SVS ON and SVS OFF with infants assigned
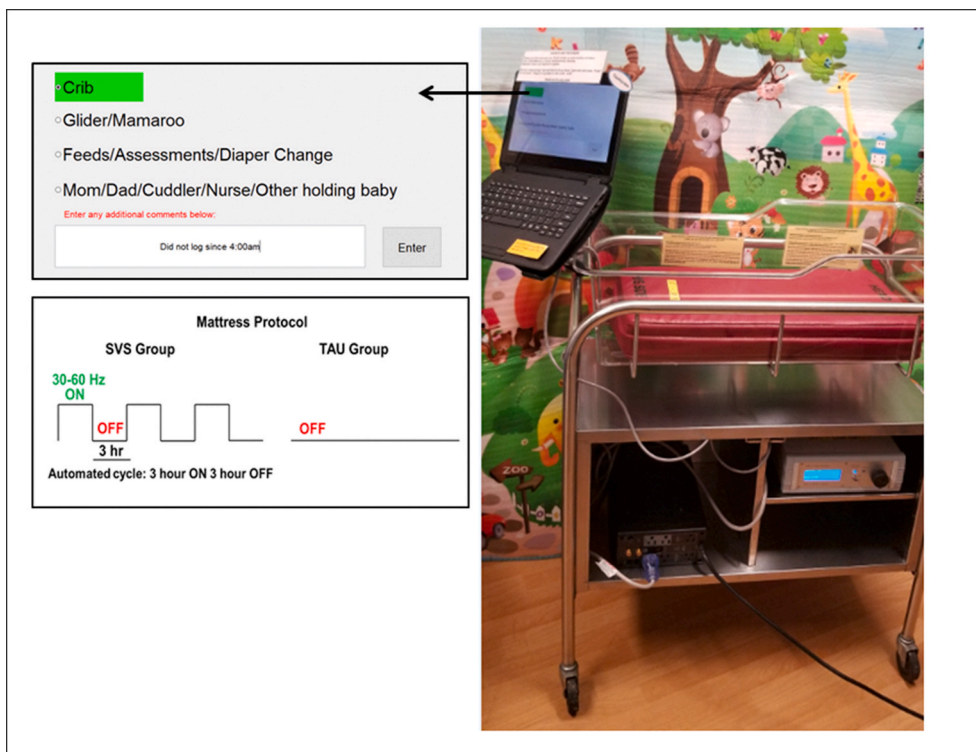

Fig. 3. Bedside Setup. SVS group = Infants randomly assigned to receive stochastic vibrotractile stimulation: SVS mattress in bedside portable crib with stimulus driver and uninterrupted power supply in crib-cart shelving; TAU group = Infants randomly assigned to receive treatment as usual (hospital crib mattress, not shown); Touchscreen computerized bedside log with laminated instructions attaches to crib; Mattress protocol indicates automated 3-hour stimulation cycle (SVS) or no stimulation (TAU).

to the SVS mattress, and between infants assigned to SVS and TAU.

2.6.5. Infant follow-up assessments post hospital discharge

Following hospital discharge, infants will be followed throughout their first year of life. Phone-call follow-up using a brief (approximately 10–15 min) standardized interview script will begin 1 week after discharge to determine any hospital readmission as well as to obtain a general assessment of behaviors and home environment. Assessments will continue bi-monthly throughout the year up until the infant is no more than 14 mos of age. Report of infant's development will also be obtained from the caregiver using the Ages and Stages Questionnaires [39] by trained study staff starting at the 4-mos phone call. Bi-monthly phone calls are also incorporated to help keep subjects engaged in the study and to promote subject retention for the in-person neuro-development assessments.

Infants will participate in comprehensive developmental assessments at approximately 6 mos and 12 mos of age (see Section 2.10 Outcomes and Table 1 for detailed description of these assessments). Infants will be assessed either on site or at home visits. Each in-person visit will last approximately 2 h and include self-report questionnaires about the infant by the caregiver. Trained neuropsychologists or developmental specialists trained and supervised by an experienced neuropsychologist (SRB) will administer and score the neurodevelopment tests. For quality assurance, the Pitt site principal investigator (SRB) who is a trained neuropsychologist and/or the senior developmental specialists (CB/EE) will review test protocols at both sites for valid administration and scoring. Development specialists will participate in routine joint-training sessions and conference calls to ensure both sites are consistently following protocol, and to problem solve any subject issues and examiner drift that may arise.

2.6.6. Maternal assessments

Biological mothers who consent to participate with their infant will complete a maternal questionnaire that includes information not available in the EMR, including detailed history of drug use before and throughout pregnancy. Biological mothers will also complete self-report questionnaires that provide a general evaluation of family relationships (McMaster Family Assessment Device [40]) and psychological distress (Brief Symptom Inventory [41]) reflective of the week preceding the birth of their infant, and at the infant's 6 mos and 12 mos assessment. A general index of the biological mother's cognitive and perceptual/reasoning skills will be assessed with the Wechsler Abbreviated Scale of intelligence –Second Edition (WASI-II) [42] at a separate visit within the 1-year study period, typically within the first few months of the study.

2.7. Measures to retain subjects and minimize missing data

Study staff will provide in-service to nursing staff at respective sites to explain study protocol and demonstrate bedside study equipment. Medical caregivers will not be responsible for managing any of the bedside study equipment but will be trained to assist in marking infant activity using the computerized bedside study log. To reduce loss of data due to technical issues, research staff contact information will be clearly labelled on the bedside equipment and study staff will be on call 24-7 to troubleshoot by phone or in person any issues with the bedside devices. Study staff will check on infants and study equipment daily throughout the infant's hospitalization. Frequent communication by study staff with subjects and medical caregivers, and daily checks at the hospital bedside of the infant and study equipment will facilitate rapport with subjects and medical staff caring for the infants. This will help ensure any concerns about infant participation are communicated and that study devices are working properly throughout the study period. Follow-up and retention is facilitated by detailed contact information including alternate contacts who may also participate in the follow-up assessments, by routine bi-monthly telephone assessments, incorporation of home visits for families with limited access to transportation, parking vouchers for

Table 1
List of assessments.

Task (time) Testing Age	Description and Respondent [Child (C) or Parent (P)]	Key Variables
FUNCTIONAL STATUS OF INFANT		
GOS-E Peds [64] (10 min) 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).	Category Score (1–8)
Pediatric Quality of Life [65] (5 min) 6mo and 12mo	The PedsQL Parent Report for Infants, age ranges from 1 to 12 months and 13–24 months. Scales assess physical function, physical symptoms, emotional function, social function, and cognitive function. Administered by Outcomes Specialist or Research Study Staff. (P)	Total Score Subscale Scores
NEURODEVELOPMENT AND SLEEP STATUS OF INFANT		
Bayley Scales of Infant & Toddler 3rd Ed [45]. (30 min) 6mo and 12mo	The Bayley III measures neurodevelopment to 3 yrs. Provides measures of cognitive function: visual preference, attention, memory, sensorimotor, exploration, manipulation, and concept formation. Fine and gross motor development are also assessed. Administered by Outcomes Specialist. (C)	Cognitive & Motor Scores Subtest Scaled Scores
Pediatric Evaluation of Disability Inventory [47] (10 min) 6mo and 12 mo	The PEDI Mobility and Self-Care domains provide standardized assessments of skills appropriate from ages 6 months to 7.5 years. Administered by Outcomes Specialist or Research Study Staff. (P)	Mobility and Self-Care Standard Scores
Brief Infant Sleep Questionnaire [48] (5 min) 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)	General Sleep Assessments
SOCIAL AND EMOTIONAL STATUS OF INFANT		
Bayley Social and Emotional Scale [45] (10 min) 6mo and 12 mo	The Bayley S&E measures social and emotional adjustment of infants and toddlers. Administered by Outcomes Specialist. (P)	Composite Score
PARENTAL INTELLECTUAL ABILITY AND PSYCHOLOGICAL STATUS		
Wechsler Abbreviated Scale of Intelligence [42] (20 min) 1mo**	The WASI II is a short and reliable measure of intelligence in clinical, psycho-educational, and research settings and is individually administered. Four subtests will be used to generate a FSIQ: Vocabulary, Block Design, Matrix Reasoning, and Similarities. Administered by Outcomes Specialist. (P)	4-Factor IQ
Brief Symptom Inventory-18 [41] (5 min) 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)	GSI Subtest T-Scores
ENVIRONMENT AND FAMILY FUNCTION OF PARENT		
General Functioning Scale [40] (5 min) 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	Total Score

Table 1 (*continued*)

Task (time) Testing Age	Description and Respondent [Child (C) or Parent (P)]	Key Variables
	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)	

Note to Table 1: 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:
1) BSI and McFad (baseline) questionnaires may be administered in hospital by research study staff to obtain baseline assessment while the infant and/or mother are still in hospital (may be performed by Outcomes Specialist at 1mo outpatient visit if unable to administer while in hospital).
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) **WASI II may be administered anytime throughout the study period by Outcomes Specialist.

subjects who participate in follow-up assessments on site, and monetary remuneration for subject's time post hospital discharge for participation in the 1-mo maternal, and 6mo and 12mo infant developmental and maternal assessments.

2.8. Data management

Primary study data (including data obtained from EMR, interviews, and follow-up assessments) are collected and managed using Research Electronic Data Capture (REDCap) tools hosted at UMass [43,44]. REDCap is a secure, web-based software platform designed to support data capture for research studies that provides: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [43,44]. To promote data quality, REDCap study forms include range checks for data values and check boxes for unknown and not-completed assessments to reduce data entry errors.

Digitized data obtained from external acquisition systems (physiologic data, Embla N700, Broomfield, CO; actigraph data, Actiwatch 2, Philips Respironics, Murrysville, PA) are processed using respective proprietary software and specially-designed programs developed by our study team. The de-identified processed data are stored on encrypted, password-protected electronic data bases. De-identified data from the electronic data bases are imported into statistical programs (e.g., SAS Institute, Cary, NC; SPSS, Chicago, IL) for analysis. Quick Base is the platform used to store subject contact information for follow-up assessments. These electronic storage databases comply with UMass data security guidelines and employ high security, controlled access points and automated incident detection and procedures to ensure secure infrastructure. Only investigators with IRB approval are assigned password-protected accounts in these environments. Data files will be archived as required by IRB and Institutional policies past the end of the study.

2.9. Data safety and monitoring board (DSMB)

The DSMB is made up of three experienced external investigators, including clinicians and a biostatistician, who provide oversight of the safety of the trial participants and of the conduct of the study. The Board was appointed by the study investigators with approval from the IRB and sponsoring agency. The Board reviews reports on safety, recruitment,

and study conduct prepared by the trial biostatistician (BB), may request additional data/information (if necessary), and advises the trial leadership regarding continuation/discontinuation of the study.

The DSMB will meet at least twice per year and possibly more frequently if the speed of recruitment warrants it. The DSMB may request more frequent reports of selected information, such as recruitment or adverse events, and, if one or more members requests, a meeting will be arranged as soon as possible. Minutes of the DSMB meetings and communications from the DSMB to the PI and to NIH will also be filed with the UMMS IRB.

2.10. Outcomes

The primary short-term clinical outcome is withdrawal severity quantified by withdrawal scores [27,35] (including max and means) and use of primary pharmacological agent (i.e., days treated and cumulative dose of morphine). Secondary short-term outcomes that will also provide an index of withdrawal severity throughout hospitalization are use, duration and cumulative dose of secondary/tertiary medications, velocity of weight gain, and length of hospitalization. In addition, physiologic data obtained from actigraphy and from the single sessions studies will provide a quantitative index of the physiology of withdrawal at different time points throughout the infant's hospitalization. The study design also allows comparison of physiologic and actigraphy differences between intervals of SVS ON and SVS OFF among infants assigned to SVS, and among infants assigned to TAU (i.e., SVS OFF).

The primary longitudinal outcome is infant neurodevelopment in the first year of life, measured by the Bayley III Scales of Infant Development [45] at 6 mos and 12 mos of age. These tests include well-established and validated measures of infant development, intelligence, and neuropsychological function and assess five functional domains: attention and executive function, language, sensorimotor function, visuospatial processing, and memory and learning [46]. Secondary long-term outcomes that will assess development in the first year of life include mobility skills [47], fine and gross motor development, social and emotional adjustment [45], and sleep behaviors [48]. See Table 1 for a list and timing of the longitudinal assessments.

2.10.1. Potential confounders, Co-factors and effect modifiers

We will obtain a comprehensive data set on the infant and mother, including maternal medical history, drug use and medications throughout pregnancy, chronic health and psychiatric conditions, pregnancy and delivery complications, and intellectual, social and economic factors (e.g., personal relationships, education level, living arrangements, work status). We will also obtain daily cares of infant throughout hospitalization including feed type (formula or breast milk) and feed route (bottle/gavage or breast-fed) and medications.

Computerized bedside log (Fig. 3) will provide an estimate of how many hours per day infants are held by caregivers, placed in hospital-issued motorized seats, or lying in crib (subsequently calculated to assess overall duration with and without SVS). This log data will also allow for comparisons between infant movement activity (actigraphy), index of irritability, when the infant is in the crib with SVS ON compared to SVS OFF.

Follow-up phone assessments will provide information about environment (e.g., biological family or placed in foster care), housing (e.g., shelter or private home), infant sleep behaviors, and socialization and supplemental care (daycare; Early Intervention).

2.11. Statistical approach

2.11.1. Sample size/feasibility

We will recruit 230 infant-mother dyads (460 subjects) over a 5-year period. At the time of anticipated start of enrollment (2016), UMass had approximately 4000 deliveries per year and UPitt had approximately 10,000 deliveries per year, with estimated 2–3% newborns diagnosed

with NAS due to opioid exposure at each site (~90 and 250 per year, respectively). At UMass, on average 75–80% of the opioid-exposed newborns typically required prolonged hospitalization for pharmacological management of NAS (primary morphine) and 20–25% were discharged without pharmacological treatment. At UPitt ~60% of the opioid-exposed newborns required prolonged hospitalization for pharmacological management of NAS (primary morphine) with 40% discharged without pharmacological treatment.

Based on conservative estimate (i.e., inability to obtain informed consent in ~50% potential candidates due to parent inaccessibility, lack of interest and custodial issues related to incarceration), we anticipated a sufficient subject pool of ~45 opioid-exposed newborns/year at UMass and ~125/year at UPitt. At UMass we estimate to enroll 25 infants/year over a four year period (100 total) with approximately 75% (19 infants/yr) requiring prolonged hospitalization for pharmacological management (estimate 75 treated in the NICU over 4 years). At UPitt we expect to enroll ~22 infants in the first year and ~36/year in years 2–4 (130 total) with approximately 60% (78 infants) requiring prolonged hospitalization for pharmacological management over the course of the study.

2.11.2. Power calculations

We anticipate sufficient sample size to detect clinically meaningful differences with 90% power, described below:

(1) In hospital short-term clinical outcomes. Given that withdrawal severity drives and guides pharmacological management, power calculations for short-term in clinical outcomes assessments were based on the commonly used Finnegan NAS score [35], the withdrawal assessment tool used to assess severity of withdrawal at both sites. Based on Nayeri [49] and our own data (Finnegan NAS score in opioid-exposed infants; SD of 2.0–2.5 [29]), assuming a standard t-test with a two-sided alpha level of 0.05 for the unadjusted comparison of the Finnegan scores using a conservative standard deviation (SD = 2.5), we estimated a sample size of 115/group can detect a difference of 1.1 with 90% power. Taking into account 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) In-hospital physiologic outcomes. Using movement duration as a primary outcome to power the physiologic single sessions based on our preliminary data in 26 NAS infants [29] (OFF: mean 40% condition time, SD = 10%; ON: mean 26% condition time, SD = 9%) and assuming a two-sided paired t-test at alpha = 0.05 for the unadjusted treatment effect, we estimated 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%).

(3) Post-discharge longitudinal developmental outcomes. For the longitudinal follow-up outcomes, power analysis was calculated for cognitive function at 12-months using Bayley-III Scales of Infant Development [45]. We anticipated an attrition rate of ~40% in the 1-year follow-up assessments. Assuming a sample size of 60 infants/group at 12 months of age with a two-sided standard t-test at alpha = 0.05 and SD of 14 for the Bayley-III Cognitive Composite Scale [50], we will have 90% power to detect a difference of 8.5 (or about a 12% difference) between the two groups. 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 (6 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 estimated 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.

2.11.3. Statistical analyses

(1) In hospital short-term clinical outcomes. Descriptive statistics will be calculated (means/SD or median/IQR) by assignment group (SVS or TAU) of outcome variables (e.g., withdrawal scores, pharmacotherapy, duration and cumulative dose, movement activity indexed by actigraphy). Because infants will be repeatedly observed and measured, initial analyses comparing outcomes between the groups 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. 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. Examples of factors of interest include: study site; drug exposure (e.g., opioid type such as prescribed maintenance therapy, other prescribed medication, and illicit substance; with or without poly-drug use), demographic data (e.g., gender, gestational age, birth weight, birth head circumference; infant race as provided by the biological mother), and feed type/route (formula or breast milk/bottle breast-fed). Comprehensive histories from medical record and questionnaires will allow us to examine the influence of additional variables. 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).

(2) *In-hospital physiologic outcomes.* Study design allows systematic quantification of condition effects on breathing (inter-breath variance and respiratory rate), cardiac rhythm (R-R variance and heart rate), movement activity (frequency and duration), blood-oxygen levels, and skin temperature. Histogram of frequency-bands of cardiac, respiratory and movement incidents will be determined. Mixed effects models will be used to examine if SVS, within SVS-assigned infants, and between SVS and TAU groups: 1) Decreases irritability indexed by movement frequency and duration; 2) Improves cardio/respiratory activity; e.g., reduces bradycardia/bradypnea, tachycardia/tachypnea and increases incidents of eucardia/eupnea; and 3) Reduces other NAS symptoms: e.g., temperature; oxygenation.

(3) *Post-discharge longitudinal developmental outcomes.* We will use a general linear model approach to analyze outcomes over one year, using the same model building strategies described in (1) above. Some outcomes, such as the Bayley-III scales [45], 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 [51] to determine how many deviant scores are required to identify an infant 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 TAU reduces likelihood of impairment.

2.12. Registration and trial status

This protocol was developed according to the 2013 *Standard Protocol Items: Recommendations for Interventional Trials* (SPIRIT) checklist [52]. The reporting of the results will follow the 2017 consolidated standards of reporting trials (CONSORT) [53] for reporting a randomized trial assessing non-pharmacological treatments. The trial was registered within ClinicalTrials.gov (NCT02801331) on June 15, 2016. Recruitment began March 2017 at UMass and August 2017 at UPitt. In-person studies (in-hospital bedside and follow-up) were halted due to Covid-19 Institutional and IRB requirements. It is anticipated that recruitment will be completed by approximately December 31, 2020.

3. Discussion

Despite rapidly rising rates of NAS due to opioid exposure in newborns over the last decade [1–3,5], there has been little advancement in improving diagnosis and treatment strategies [15]. The aim of this trial is to assess the effectiveness of SVS for reducing drug withdrawal in opioid-exposed newborns and for improving long-term developmental outcomes. The hospital setting provides a unique opportunity for studying the onset, duration, and severity of symptoms and dysregulated behaviors associated with NAS, and for advancing new strategies that improve short-term clinical outcomes and promote healthy neonatal development. In this clinical trial, withdrawal will be assessed by several measures, including standard clinical withdrawal-severity scores, physiologic recordings, and actigraphy. In-hospital outcomes (e.g., withdrawal scores, cumulative morphine, length of treatment, velocity of weight gain) and 6-month and 12-month follow-up (masked neurodevelopmental assessments) will be compared between infants assigned the SVS mattress intervention and infants assigned the hospital mattress, with the overarching goal to optimize diagnosis and management of opioid-exposed newborns.

To assess risk factors that may be associated with NAS, this proposal is designed to include multi-parametric data such as demographics (e.g., gender, race, gestational age, weight) and drug history (e.g., single opioid versus opioid plus other drug exposure). Although the general symptoms and physical signs of withdrawal tend to be relatively similar regardless of drug/s of exposure, the onset, duration and severity of opioid withdrawal are highly variable and unpredictable [10,12,54,55]. In this trial, we will obtain comprehensive medical information on the biological mother and infant, including toxicology reports and daily EMR data regarding infant withdrawal scores, medications, feeds and weight that will allow us to track severity of withdrawal, course of treatment, and clinical outcomes throughout hospitalization. We will also obtain detailed history of drug report from interview with the biological mother, which may provide unique insight on outcomes related to type and timing of drug exposures throughout the prenatal period.

It is well documented that fetal exposure to opioids commonly disrupts central, autonomic, vasomotor and gastrointestinal function in the newborn [7,12,13,17,36,56,57]. However, there is a paucity of research on the physiology that demarcates neonatal drug withdrawal in the first weeks of life. Furthermore, despite lack of well-defined characterization of physiologic withdrawal, potent analgesics (e.g., morphine, methadone), central-nervous system depressants (e.g., phenobarbital) and hypertensives (e.g., clonidine) with well-documented long-term neurodevelopmental consequences are commonly used to treat opioid withdrawal in neonates [23,36,54,58–60]. Complementary, non-pharmacological interventions are needed to treat NAS and reduce use of these intoxicating medications. In this comprehensive clinical trial, we will study physiologic activity (e.g., cardiac, respiratory, blood-oxygenation, temperature, limb movement) in a cohort of infants at around 5–7 and 12–14 days of life. This data will provide objective quantifiable measures of physiologic withdrawal among newborns at two consistent time periods and assess whether physiologic indicators (e.g., cardio-respiratory pathophysiological instabilities; excessive movement) are reduced with SVS. Cofactors that may optimize the effectiveness, or exacerbate withdrawal, will also be assessed.

A major aim of this proposal is to test the hypothesis that SVS reduces NAS morbidities and enhances neurobehavioral development throughout the first year of life. There are very few longitudinal studies on neurobehavioral consequences of intrauterine opioid exposure [60–62]. Those available have conflicting results that can be attributed to variations in poly-substance use including type, quantity/dose and duration, maternal psychiatric morbidity, prenatal care and obstetrical complications, homogenous and small populations of subjects, type and duration of treatment including pharmacological interventions and mother-child interactions, quality of the assessments and use of different neurobehavioral tests at different ages [60,63]. Neurobehavioral outcomes in neonates exposed to drugs are also likely influenced by socio-demographic, biological, health and economic factors [60,63] Our testing measures take these variables into account (see Table 1) [40,63]. Because opioid-exposed infants are susceptible to poor outcomes due to biological and environmental factors, it is especially important to develop strategies that provide early intervention to promote healthy development. An important goal of this project is to determine whether early therapy with SVS puts at-risk infants on a trajectory for improved outcomes compared to infants receiving TAU. We will follow infants bi-monthly via caregiver report and at in-person assessments by trained outcomes specialists at 6-mos and 12-mos to help differentiate among short and longer-term deficits.

This project brings together established investigators and expert clinicians to conduct a dual-site, prospective longitudinal study in newborns exposed to opioids *in utero*. The advantage of studying infants at two sites is that we will be able to test the effectiveness of SVS as a therapeutic intervention in a large population of infants, encompassing a wider range of demographics, drugs of exposure and standard-care practices. SVS will be initiated shortly after birth and administered daily throughout hospitalization. Findings from this trial will improve understanding of withdrawal in opioid-exposed newborns, and will determine whether SVS, compared to TAU, reduces severity of NAS, attenuates the need for pharmacotherapy, and improves physiologic function with associated improved long-term cognitive, behavioral and health outcomes.

Declaration of competing interest

Dr. Bloch-Salisbury is an inventor on a patent (PCT/US2015/021999) licensed to Prapela, Inc related to the SVS-mattress device and is a potential beneficiary of a licensing agreement with Prapela, Inc.

The authors have no other financial relationships relevant to this article to disclose.

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