NCT03881553 Study Protocol and Statistical Analysis Plan

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NCT03881553: Interventions to Help Infants Recover in Hospital

Study Protocol and Statistical Analysis Plan v.071020

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1. TITLE
NCT03881553: Interventions to help children recover in the hospital.

2. EXTERNAL IRB REVIEW HISTORY*
N/A

3. PRIOR APPROVALS:

Conflict of Interest (COI):
The PI (Salisbury) is a co-inventor on a patent for the stochastic vibratory stimulation (SVS) mattress device, which will be used in this project. There is an approved mitigation plan in place at UMass due to a potential financial conflict of interest.
COI Mitigation Approval Letter uploaded on eirb.

Clinical Engineering Department:
Medical and research devices with power sources will be inspected for safety, including grounding and minimal current leakage as necessary, prior to being placed in service and will be inspected annually by the Clinical Engineering Department. The Clinical Engineering Department Electrical Safety Inspection protocol shall be used as the inspection procedure. All measurements shall meet the NFPA 99, IEC 60601 healthcare standards for electrical safety. All medical devices with power sources regardless of ownership shall be inspected for safety, including grounding and minimal current leakage as necessary, prior to being placed in service.

Upon receiving new equipment with power sources for use in the study, a study investigator will notify the Clinical Engineering Department at 508-334-1111 directly, or through the Materials Management Department, regardless of the purchase rental, loan, lease, evaluation, or demonstration arrangement. The outside manufacturers/ contractors are responsible for the quality and performance of all rented, leased, contracted, or equipment on evaluation.

Biohazardous Agents:
• N/A

Radiation*:*
• N/A

4. PROCEDURES INVOLVED
Randomization: Subjects will participate in up to four study sessions that include NEATCap intervention and/or SVS mattress intervention based on duration of subject's hospitalization, availability of research personnel, availability of device and fit-ability of the device around the head and ears of the subject (currently we have 4 sizes, but additional sizes may become available during the study period). Subject will serve as his/her own control, and will receive alternating periods of intervention ON vs intervention OFF.

- *Devices: Purpose of use and regulatory approval status (***see also section 32***)*. The two experimental devices used in this study are Abbreviated IDEs:

  1) NEATCap Device: The NEATCap ("Dreamies") device is an experimental device engineered by NEATCap, LLC (patent pending). It is a circumaural passive noise protection device comprised of a soft fabric headband with a specially-designed ear covering that simulates the acoustic filtering of a pregnant mother's body. The device was designed to dampen unsafe, high frequency noises (e.g., alarms from medical equipment) while allowing passage of low frequency sounds such as a caregiver's voice. There are no electrical components to this device. The device is a circumaural hearing protector, FDA product code EWE [510(K) exempt device], which as per FDA rulings does not require IDE to test before the device is marketed; see: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=EWE]. The predicate device for NEATCap "Dreamies" is MiniMuffs Neonatal Noise Attenuators, marketed by Natus Medical since 1995 that has been used on NICU infants in high-noise situations for many years. Indications for use state "The device is intended for use on newborns to provide reduction in the sound level reaching the newborn's ears." The proposed studies in this docket involves non-invasive measurements with NEATCap device, also an EWE circumferential hearing protector device, for up to four session periods, not to exceed 24 hours in any one period.

  2) SVS Mattress Device: The SVS mattress device is an experimental device. It will be used to gently stimulate the subject. The specially-constructed mattresses are similar to the usual hospital mattress except that inside the mattress foam there is a device that vibrates the foam, controlled by an external unit. The mattresses are constructed by Cofab Design, LLC or other contracted company using patent specifications, modified to adjust for various size cribs and beds. The device components in the mattress and external control unit may be modified with improved technologies to allow for testing of various displacements and mattress sizes, and to help ensure consistency of mattress integrity over time. The mattresses are designed so that the foam vibrates throughout the entire mattress. We are aware of no deleterious effects of the SVS mattress. We have studied over 100 premature infants (since 2001) and over 50 infants exposed to opioids *in utero* (since 2010) using the SVS mattress without incident or apparent side effects. The FDA has not approved the SVS mattress as a treatment for prematurity or withdrawal. Sound level produced by the mattress will be monitored and will not exceed 75 decibels (60-70 dB is normal conversation; 75 dB is about the sound of an average car interior on a highway). The UMass/Memorial Health Care Biomedical Engineering will certify the electrical safety of the mattress devices.

- *Research procedures:* Subjects will participate in up to four sessions, applying either the NEATCap and/or SVS mattress. Sessions will last on average between 8 and 12 hours, and will not exceed 24 hours in any one session. All sessions will

be performed at the subject's NICU/CCN or PICU/PIU bedside. Infants and children enrolled in this study will receive routine, standard of care, which may include pharmacological management as prescribed by their primary medical caregiver complementary to the intervention (NEATCap; SVS mattress). Nurses are instructed to provide routine care and to intervene as they would typically do despite the presence of an investigator by the bedside.

Standard measurements and recordings**.** Physiologic recordings with and without electroencephalographic (EEG) activity will be obtained through state-of-art acquisition system (e.g., Embla, Nihonkohden or other) obtained (hardcopy) or recorded (digital) directly from hospital monitor (e.g., Philips, ixTrend or other). Respiratory inductance plethysmography (RIP) will be used to measure breathing. Respiratory belts will be placed around the chest wall and/or abdomen to record respiratory muscle movements, and allow for detection of inter-breath intervals (IBI) of respiration. Sensors over the skin surface of the torso will be used to record electrocardiographic activity (ECG), and allow for detection of R-R intervals of the ECG signal (index of inter-beat heart rate). Electrodes over the head and face area will be used to measure EEG activity at the surface of the cortex to allow for sleep stage classification using EEG signal analysis; electrode impedance will be measured to help ensure data quality. A probe attached to the foot or wrist will measure arterial-blood oxygen concentration; quality of the plethysmographic activity characterized in the pulse signal will allow for identification of movement periods. Movement periods will be assessed further via actigraphy with a wireless sensor worn around the infant's leg and/or arm that records limb movement. Skin temperature will be measured continuously with a sensor placed under the armpit or back. A sound and light meter placed near the head will record sound frequency and intensity, and changes in light level. Overt behavioral data will be recorded using a camera with a wide-angled lens placed within or near the subject's bed. Medical history (including toxicology screens) and demographic data will be obtained on the infant/child and on the biological mother by manual medical record review or electronically extracted via UMCCTS Data Lake.

Data acquisition, recording and archival. Physiological data will be digitally recorded (~50-1kHz samples per channel) using bedside data acquisition system or recorded directly from hospital bedside monitor onto secure research computer/laptop. Acquisition 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. Movement will also be digitally recorded independent of the full-acquisition system using wireless actigraphy sensor. All signals, video images and germane data (e.g., medical histories) will be stored on encrypted, password protected computers. Investigators will also manually record relevant study information (timing and mode of experimental conditions, nursing assessments, feeds, medications etc) on log sheets. A log (computer or pen and paper) of the infant's/child's daily activities and nursing interventions will also be obtained, along with relevant clinical information (feeds, withdrawal scores, medications) obtained from electronic medical record for the study session day

and up to one day preceding and following each study session.

Study Sessions**.** The study will be conducted in the UMass Memorial NICU/CCN and in the UMass Memorial Children's Medical Center PICU/PIU. The subject will be studied in the unit in which he/she is receiving care. Enrollment in this study allows the subject to participate in up to 4 full-recording study sessions throughout their hospitalization. A full-recording study session will typically last approximately 8-12 hours (~8am-6pm or ~8pm-6am); some sessions may start earlier/later or go shorter/longer and in some instances we may study the subject for 24 hours (based on research personnel and equipment availability). The reasoning behind a shorter session and for having morning and evening start times is that as the subject matures, s/he may have 'wakeful' periods that prevent study in the crib/bed for certain periods throughout the day. The reasoning behind a 24-hr period is if we have available research-personnel support, we may study a subject throughout a complete 24-hr period to obtain diurnal responses. The number of full-recording sessions the subject participates will depend on duration of hospitalization (e.g., some subjects may be in the hospital longer than others, which will allow more opportunity to participate in multiple study sessions), on availability of research equipment and research personnel, and parent/guardian schedule (e.g., parent/guardian may prefer we not study the subject on certain days, for example if they want to spend time holding the subject or have visitors throughout the day). We will review the infant's/child's medical records and we will obtain additional history through questionnaire from the consenting parent/guardian. We will also obtain medical history on the subject's biological mother, including questionnaire and review of maternal medical records, if available through the UMass Memorial Healthcare system.

Sessions will begin during the infant's/child's feeding, assessment or wake period, during which time sensors for the full-physiology/polysomnography recording will be applied by research study staff; sessions may begin any time if recordings are obtained directly from the bedside monitor. Periods of no intervention (NEATCap device OFF or SVS Mattress OFF) will be alternated with periods of intervention on (NEATCap device ON or SVS Mattress ON). The duration of each intervention period will conform to the routine care of the study subject. Because feeds vary as a function of subject's age, for example premature infants are typically on a fixed ~every 3-4 hours, whereas older infants and children may feed ad-libitum (i.e., as the child desires), the duration of intervention ON and OFF will vary within and between sessions and among subjects. The hospital standard of care for an individual subject, and the subject's sleep/wake cycle will determine the duration of the intervention periods. For subjects who may sleep throughout the night, periods of intervention will conform to either a routine assessment or medication interval (typically ~ every 3-4 hours) to allow for comparisons between intervention ON and intervention OFF with minimal disruption to the subject. The OFF-ON alternating cycles allow subjects to serve as their own control and ascertain if intervention ON leads to consistent, positive responses in the same subject, and assess whether the effect changes over the period.

NEATCap Intervention: At feed/assessment/wake period preceding a

NEATCap ON period, the NEATCap device will be fitted and placed on the child by research study staff. The NEATCap device will be removed (OFF) and replaced (ON) at alternating intervals throughout the study session. Physiological data will be recorded throughout the session while the subject is in the crib/bed or hospital-issued sleeping environment (e.g., motorized seat).

SVS Mattress Intervention: At the start of the study session (during a feed/nursing intervention/wake period), the subject's hospital mattress will be replaced or covered with the SVS mattress. For bedside studies in babies cared for in infant crib-warmers that have low guard walls, SVS mattress bedframe extenders (Cofab Design, LLC) will be attached to the guard walls of the infant crib-warmers for the duration of the study session. These bedframe extenders will extend the guard wall 2 inches, the height difference between the SVS mattress and the standard crib-warmer mattress. The study staff will turn the external mattress controller off (SVS Mattress OFF) and on (SVS Mattress ON) at alternating periods throughout the study session. Physiological data will be recorded throughout the session while the subject is in the crib/bed with the SVS mattress.

- *Data to be Collected:* Infant/Child subject and biological maternal medical histories including maternal drug use during pregnancy (if applicable), infant/child daily clinical care measurements (feeds, medications, withdrawal scores), and analyzed data (i.e., scored sleep studies; actigraph and physiological data) comprise the data obtained from subjects. Data may be obtained directly from infant/child medical record, maternal medical record, and/or questionnaire administered to person/s providing informed consent. All data will be collected solely for the proposed research studies.

- *Medical record review:* Subject's medical records will be reviewed and additional history will be obtained from parent/guardian, including review of biological mother medical records if in the UMass Memorial medical record system. We may review medical records throughout the infant's/child's hospitalization and for up to 1-year post hospital discharge. Study staff may review medical records for information pertinent to this study enrollment period until the study is closed out. We request protected health information from general medical records and review of statutorily protected records at this institution to: 1) Make sure the infant/child meets inclusion criteria; 2) Obtain toxicology reports indicating drugs of exposure and other relevant records pertaining to NAS and/or iatrogenic drug withdrawal; 3) Obtain information about factors that may influence the physiological function of the infant/child (e.g., prenatal and postnatal care and prenatal drug exposures; critical-care illness for which the child is being treated in the NICU/PICU, and post-discharge followup). We request to review both the infant's/child's and mother's medical records for information from cardiac studies, nursing and respiratory therapy notes, clinical monitor information, intake and discharge summaries, daily assessments (feeds, medications, withdrawal scores), EEG/EMG studies, laboratory results, operative procedures, conclusive pathologies, clinical problem

list, and pulmonary, radiology and rehabilitation information. Data collected will be stored on REDCap forms.

- *Covid-19 Related Procedures:*
  In accordance Joint UMCCTS_IRB Covid-19 Guidance v2 031720, we restricted human subjects-related research as follows:
    1. Halted enrollment
    2. Halted all in-person bedside studies

  As per IRB and CCTS Guidelines and Job aid for reopening human subjects' research during the Covid-19 pandemic, the following procedures will be employed upon IRB approval to resume in-person research studies to help ensure the safety of study participants and their families, research staff, and personnel involved in the care of the infant throughout study enrollment. Research study staff will comply with ongoing Institutional Covid-19 requirements and adhere to unit safety precautions.
  Approval has been obtained from study safety officers and medical caregivers in clinical departments to resume studies in infants' respective units where the bedside studies are conducted with the following procedures:

1. **Recruitment:** We will continue to identify subjects through medical record (HIPAA waiver in place) and obtain approval from subject's medical caregiver within the subject's unit department for approaching candidates who meet criteria. Any known COVID-19 positive patients will be excluded from study.
2. **Consent of new study subjects:** Given that infant-subjects are in-hospital at time of consent, in-person consents will be obtained via current process with the following additional Institutional recommended Covid-19 safety measures by research staff: e.g., social distancing, masks, hand-washing. Writing pens will be wiped with Institutional-hospital cleaning/sterilizing wipes before and after obtaining each hard-copy signature. Remote consenting procedures as per Job Aide for reopening humans subjects' research guidelines may be used in instances when study staff is unavailable to consent in person (e.g., Due to Covid-19 Institutional restrictions on number of personnel allowed in office on a given workday, research personnel with consenting privileges may not be on site at a time conducive to obtaining timely consents). Verbal informed consents in hospital may be conducted via electronic video-chat/zoom/call, and may be obtained from subject by research staff within the consenting time frame. Hard-copy signatures will be obtained from the subject and researcher obtaining consent, or by another researcher with consenting privileges who subsequently reviews the consent with the subject in person prior to start of any intervention.
3. **Bedside Studies:** We will follow Institutional unit Covid-19 safety protocol for cleaning/sanitizing bedside study equipment, devices, and sensors that are not disposable (e.g., mattress, study cables, bedside laptops, ipads, actigraph, pens). We will abide by all unit safety precautions for infant and adult participants, including caregivers who have in-patient privileges with the in-patient infant. For adult subjects/caregivers who are in hospital and participating

in study questionnaires on behalf of themselves and/or their infant at the bedside, research staff will comply with all unit safety requirements. Questionnaire testing materials (e.g., pens, ipads, clip boards) will be cleaned before and after use with hospital sanitizing wipes. Adult subjects will wear gloves while completing paper/electronic questionnaires. Research staff will comply with unit safety measures, e.g, mask, gown and glove, during bedside sessions, in addition to routine hand washing and hand sanitizing.

5. DATA AND SPECIMEN BANKING*

REDCap will be used to store research data stored as subject code (PHI such as infant/child and maternal medical histories, daily clinical care measurements) and analyzed data (i.e., scored sleep studies; actigraph and physiological data). Physiological and environmental (light/sound) data collected on acquisition system and actigraph data may also be stored on excel worksheets on password protected computers for post-hoc analysis.

It is possible that the data will be shared with collaborating investigators (e.g., engineers and programmers) to assist with signal processing and analysis, with the NEATCap device manufacturer and/or other manufacturers who may be involved with the development or commercialization of either devices, and investigators not associated with this project. If so, all data will be stripped of all identifiers (anonymized) and subjects' identity will be unknown to these personnel. De-identified information may be made available in the future for the research community using NIH-sponsored websites, in accordance to NIH mandated data sharing policy. Any investigator contacting us for such data will be directed to the appropriate website(s), which has detailed instructions on the use of the data in accordance with NIH policies. Subject may choose to have research data anonymized at any time during or at the end of the study by contacting Dr. Elisabeth Salisbury at 508-334-8627 (or via email at Elisabeth.salisbury@umassmed.edu).

- *Disclosure of Research Results*: This study is for research purposes only. Individual results will not be given back to study participants nor will individual results go into subjects' medical record. In the short term, we do not anticipate that any clinically or diagnostically important information can be learned from this research, although such information could eventually be forthcoming.

6. DATA ANALYSIS AND MANAGEMENT*

Statistical Procedures and Power Analysis.

Study design will allow systematic quantification (mean and variance) of the effects of NEATCap device and SVS mattress on automatic function, such as breathing (IBI), cardiac rhythm (R-R), frequency and duration of body movements (e.g., defined via streamlined video, artifact in pulse-oximeter plethysmographic activity, and actigraph count), blood oxygenation (e.g., durations<85%), skin temperature, and sleep states. Analyses will be conducted to determine whether interventions impinge on neural oscillators that drive breathing and cardiac control, and whether NEATCap device reduces dangerous levels of environmental noise, to improve autonomic function and sleep activity.

Signal processing algorithms will be used to characterize separately the instability of physiological signals, such as respiration and heartbeat. We will explore, for example, whether different durations of movement periods (e.g., 1.5-5 sec; >5 sec; >10sec) have unique relationships with withdrawal (NAS or iatrogenic) or prematurity, and are affected differently with different interventions (NEATCap device and SVS Mattress).

Parametric tests will be used for analyses of all continuous variables.The Friedman's and Wilcoxon signed-rank tests will be used for nonparametric analyses. For analyses of parametric data separate repeated measures ANOVAs will test effects of stimulus condition (ON or OFF) and trial order. Post-hoc pairwise t-tests will determine differences in responses for conditions of stimulation ON and OFF. For example, separate repeated measures ANOVAs will test effects of stimulus condition (ON or OFF) and trial order on physiological variables. Time of intervention (e.g., infant age, severity of NAS) will be a covariate to assess whether there are critical periods in infant development for optimizing the intervention as a therapeutic strategy. Pearson product-moment correlation coefficient analysis will be used to establish associations between breathing stability (IBI variance) and movement duration, with the expectation that greater variance in respiratory parameters will be positively correlated with excessive movement. *P* values of <0.05 will be considered significant.

The number of periods and duration of intervention will not always be the same for each study session. The proposed study will test if different modes (NEATCap; Mattress SVS) affects duration of the interfeed interval, improves autonomic function, and promotes sleep. This is a within-subjects design, so all subjects will receive intervals of routine clinical care in addition to the assigned intervention/s complementary to routine care. Intervention assignment for study session is based on equipment availability, research personnel availability; it will not be determined by the subject's treating physician.

- It is possible that a subject does not receive an intervention (participate in a study session) after enrollment if: 1) We have technical difficulties and are unable to conduct studies; 2) Subject is discharged before being entered into an intervention stimulation session; 3) Doctor treating child requests we terminate the study – we will heed to the discretion of the Attending Physician or primary medical caregiver for decisions regarding termination of an infant from the study for example due to sickness, sepsis or exacerbated withdrawal symptoms (e.g., seizures) – such population of subjects will likely already be excluded by the exclusion criteria, but others unknown at this time may also ensue. Medical criteria for terminating a subject from the study will be determined by the medical caregiver treating the infant. Authorized parent, nurse or investigator may stop/postpone a study session for reasons such as excessive symptomatology preventing ability to properly study the subject (e.g., unable to keep sensors in place, infant needs to be held incessantly, skin rash), parent has visitors or simply doesn't want an infant/child studied on a particular day – this would not result in termination from the study per se. If we find that a mode of stimulation appears to make the infant/child irritable (e,g., excessive waking, crying, movement), we will end the study session for that day. If this happens on a second study-session day, we will discontinue study.

7. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

An independent medical safety monitor will review serious adverse events reported to the IRB and will summarize each in a written report that will be submitted to the Center for Advancing Point of Care Technologies (CAPCaT) for any required reporting to NIH.

This research does not involve more than minimal risk to subjects. While it may be difficult to determine whether NEATCap or SVS mattress causes worsening of physiological function or is related to common system dysregulation of the subject, a study may be discontinued at any time if the investigators or the subject's medical caregiver suspects there are any adverse effects on breathing, heart rate, thermoregulation, oxygenation, movement or any other function.

Nurses are instructed to provide routine care and to intervene as they would typically do, e.g., in the event of a prolonged apnea, bradycardia or blood-oxygen desaturation, despite the presence of an investigator by the subject's bedside. The protocol may be ended if intervention is associated with noticeable exacerbation of irritability including disproportionate awakening, cardio-respiratory instabilities, and/or excessive rise in temperature as observed by a medical caregiver, researcher, or parent at bedside during a study session. Parent/Guardian or medical staff may terminate the study (subject withdrawn) or request not to part-take in any procedure/s at any time (subject remains in study). Our studies are conducted at the bedside so we are in frequent contact with the clinical staff; we will routinely seek informal feedback from the medical-care staff to ensure the safety of our study protocols. The medical-care staff and parent/guardian are encouraged to call us if they have any specific concerns throughout the study enrollment.

- *Confidentiality and Data Management*: In all research records, reports and publications of the study data (including medical history and physiological signals) de-identified alpha-numeric study code will identify the subject. This code will be kept in a central database on a password protected PC. Username and password are required to unlock all research-related computers; additional passwords are used for files containing the study code that identify the subjects and de-identified data files. Only research study staff will have access to the identifying file. Any hard-copy data will identify subjects only by study code, and will be kept in a locked file cabinet. We may share de-identified data with other collaborating investigators, individuals or companies/entities in order that they may assist us with signal processing, analysis and interpretation The authorized parent/guardian may choose to have the research data anonymized at any time of the study; it will not be possible to destroy data that has already been used in analyses and data for investigational devices is required to be maintained under FDA regulations.

  To help protect subject privacy, a *Certificate of Confidentiality* (COC) has been issued by the National Institutes of Health in accordance with NIH COC Policy (NOT-OD-17-109; see https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html; and https://grants.nih.gov/grants/policy/nihgps/html5/section_4/4.1.4_confidentiality.htm). With this Certificate, researchers cannot be forced to disclose information that may identify a study subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This Certificate allows the

researchers to resist demands for identifying information with the following exceptions: 1) The Certificate does not prevent investigators from mandate reporting to health officials certain communicable diseases required by state law or local law; 2) The Certificate does not prevent investigators from reporting to authorities any knowledge of child or elder abuse, and/or intent to hurt oneself or others. The Certificate cannot be used to resist a demand for information from the US Government that is used to audit or evaluate federally funded projects. There is also information that must be disclosed to the FDA. Infants at risk for NAS due to exposure to drugs *in utero* are identified to the study investigators by physicians treating the infants. The infant's medical team is responsible for relevant mandatory reporting.