RESTORE RESILIENCE IN CRITICALLY ILL CHILDREN – R2

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Study Summary

Title	RESTORE Resilience in Critically Ill Children – R2
Short Title	R2
IRB Number	828061
Methodology	A prospective cohort study with a convenience sample of patients admitted to the PICU at two study sites.
Study Duration	Study participation will be completed at PICU discharge or PICU Day 28, whichever occurs first.
Study Center(s)	This is two-site study, CHOP & Johns Hopkins.
Objectives	The study design will allow investigators to describe usual care in each PICU and identify the facilitating and restraining factors impacting the implementation of R2 at each PICU. The purpose of this pilot study is to improve the care, environment, daily routine and sleep patterns of children in the PICU. The goal of this study is to learn what can be improved to support a critically ill child's healing and circadian rhythms.
Number of Subjects	Each site will enroll 10 baseline (control) subjects and 20 intervention subjects.
Main Inclusion and Exclusion Criteria	**Inclusion Criteria**: PICU admission at one of the study sites in which elements of R2 are typically but sporadically implemented; Between the ages 6 months and 18 years at the time of enrollment; Intubated and mechanically ventilated within the last 48 hours; acute lung disease is the primary reason for intubation; ≤4 nights in the hospital (≤2 nights in PICU); Parental/Guardian provides primary care for child; **Exclusion Criteria**: ; child has a baseline cognitive dysfunction ≥4, measured by the Pediatric Cerebral Performance Category (PCPC); Transferred to the PICU from another hospital unit/ward ≥4 days (≥2 nights in the PICU); admitted with an uncontrolled seizure disorder, cerebral hypertension, neuromuscular respiratory failure, ventilator dependence (excluding BiPAP or CPAP at night); history of inability to tolerate bolus;. enteral feeds; the presence of any of the following within 24 hours of admission: modal pain scores > 4; persistent hypotension/hypertension unresponsive to standard therapies; use of High Frequency Oscillatory Ventilation or Extracorporeal Membrane Oxygenation; administered melatonin within the past week or have active do-not-resuscitate plans.
Intervention	During the intervention phase the following will occur: 1) parents will complete the Child's Daily Routine and Sleep Survey, 2) cycled day-night lighted and modulation of sound will be provided to match the child's routine (provided by the parent), 3) the subjects sedation will be managed using the RESTORE process that is standard care at both sites, 4) night fasting with bolus enteral daytime feedings will be administered per child's routine feeding schedule (unless contraindicated), 5) the PICU Up! program will be implemented, 6) the number of nurses assigned to care for the subjects will be limited, and 7) parents will be asked to complete a paper or electronic diary during the child's PICU stay to track the day's events, their thoughts, or questions they may have for the care team.

Statistical Methodology	Descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Data will be examined for skewness, outliers, and systematic missing data. For non-normal continuous outcomes, we will consider data transformations or nonparametric methods, as appropriate. **Our primary analysis** will compare the circadian activity ratio post-extubation between Baseline Phase and Intervention Phase patients using t-tests or Wilcoxon rank-sum tests, as appropriate. **Secondary analyses** will use linear regression to control for variables that could be associated with outcomes, such as patient severity or age group. Analysis of secondary outcomes will use t-tests or Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. Regression methods (linear, logistic, proportional hazards) will be used to assess the effects of covariates on secondary outcomes. Though we do not anticipate differences due to gender, race/ethnicity, or center, we will assess main effects and possible effect modification due to these factors using regression methods. Data analyses will be performed using SAS® or similar statistical packages.
Data and Safety Monitoring Plan	This PI and data coordinating site (Children's Hospital Boston) will be responsible for data quality and safety of all subjects.

Background and Study Rationale

This is a research study and will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations as applicable.

1 Introduction

Maintaining a child's circadian rhythm during their critical illness may strengthen their resilience and, in the very least, not burden a child's already compromised state. Optimizing CR during critical illness has been shown to be feasible and safe, improve patient-important outcomes, and is therefore now recommended as one of the best practices and priorities among adult ICUs. Although each R2 element is currently practiced in 58 PICUs, the R2 bundle has not been systemically implemented or tested. The first step in a paradigm shift is to ensure there is supporting evidence for the planned change in care. Therefore, a systematic approach is urgently needed to optimize the healing milieu in the PICU and characterize the functional changes that occur as a result of disrupted circadian rhythms in PICU survivors. Our interprofessional team believes that PICU care and environments can be modulated to sustain a child's circadian rhythm (CR), support their physiological resilience and enhance their capacity to heal. The recent completion of the RESTORE clinical trial (HL086622, PI Curley) provides evidence that critically ill children can be safely managed in a more awake state. Pilot work on PICU Up! (PI: Kudchadkar), an intervention promoting early progressive exercise and mobility in critically ill children, supports its safety and feasibility. We believe that more awake, responsive and active children who receive CR-restoring interventions may derive benefit. Our team, with expertise in pediatric critical care nursing, medicine, sleep, and pharmacology intends to shift the current PICU paradigm from potentially toxic to healing for the most vulnerable of patients. It is hypothesized that patients managed per **RESTORE resilience** will experience a more restorative circadian rhythm evidenced by an improved temporal sleep-wake pattern than patients receiving usual care. The overall aim of this study is to pilot test an individualized bundle of clinical care, RESTORE resilience (R2), in pediatric patients on mechanical ventilation for acute respiratory failure.

1.1 Background and Relevant Literature

Each year, more than 250,000 infants and children in the US receive care in a PICU, and more than 100,000 are supported on mechanical ventilation (MV). (8) With improved mortality, the focus of PICU care has shifted to patient and family morbidity and improvement in quality of life. (9-11) In adults, we

know that disruptions in CR may impair mentation, immunity, autonomic function, endocrine activity, hormonal signaling, and ultimately healing.(12-15) As acuity of illness increases, circadian rhythmicity may be abolished.(16,17) Causes of circadian disruption may be environmental or internal to the patient.(18) For example, inadequate daytime illumination and increases in nocturnal light, coupled with sudden and frequent peaks in noise with high baseline noise levels, negatively impact both sleep onset and sleep continuity in the ICU. Intrinsic causes of circadian disruption include critical illness itself and the patient's experiences with distress and pain. Moreover, melatonin is integral to the maintenance of circadian rhythms and regulation of sleep, and derangements in melatonin secretion among adult ICU patients are associated with sleep disturbances. (12,16,18-24) In pediatrics, sleep recommendations are age-based and reflect neurologic maturation.(25-29) While we know that sleep quality is poor in the PICU, data regarding the clinical effects of sleep disturbances in critically ill children are severely lacking.(25,30-32) Thus, it is not surprising that a recent survey of pediatric intensivists revealed that the vast majority of PICUs do not have protocols in place for sleep promotion.(33) Currently, PICUs are implementing delirium screening with little data to support interventions for delirium prevention. This practice is disconcerting because CR/sleep disruption is a known contributor to ICU delirium. (13,34) Without data on the physical and psychological benefits of sleep in sick children, long-established hospital routines will continue to disrupt circadian rhythms in critically ill children.

2 Study Objectives

The first step in this program of research is to pilot-test **RESTORE resilience** (**R2**), a 7-item individualized bundle that we hypothesize will restore CR in critically ill children using a pre-posttest design. Two separate PICUs will each enroll 10 baseline subjects followed by 20 intervention subjects, 6 months to 18 years of age, who are intubated and mechanically ventilated for acute respiratory failure. Specifically, as soon as possible after PICU admission, parents will be interviewed to create an individualized chronotherapeutic bundle to include (1) focused effort to replicate the child's pre-hospitalization daily routine (bedtime/wake time, bedtime/arousal routine, nap time, feeding schedule, active periods), (2) cycled day-night lighting and modulation of sound to match the child's routine, (3) minimal yet effective sedation using a nurse-implemented goal-directed sedation plan (RESTORE), (4) night fasting with bolus enteral daytime feedings, (5) early, developmentally-appropriate, progressive exercise and mobility (PICU Up!), (6) continuity in nursing care, and (7) parent diaries. The overall objective of this study is to pilot-test an intervention that can be implemented in any PICU that will improve sleep-wake patterns with restoration/maintenance of circadian rhythms in critically ill children with acute respiratory failure. Results of this pilot study will be used to inform the design of an adequately powered multicenter randomized trial of R2.

2.1 Primary Objective

- Circadian activity ratio (daytime activity/total 24-hr activity) after endotracheal extubation.

2.2 Secondary Objectives (if applicable)

- Salivary melatonin levels on PICU day two and five
- Nighttime EEG slow-wave activity during endotracheal intubation with EMG and EOG
- R2 feasibility, adherence, system barriers
- Levels of patient comfort: PICU days free of pain, agitation, delirium, iatrogenic withdrawal
- PICU exposure to sedative medications (total dose and length of exposure)
- Time to physiological stability (time on vasoactive medication, duration of mechanical ventilation, PICU and hospital length of stay)
- Parent perception of being well-cared-for

3 Investigational Plan

3.1 General Design

The study design is a two-phase prospective cohort study. Consecutive subjects will be enrolled into the Baseline Phase and then the Intervention Phase in two separate PICUs: Children's Hospital of Philadelphia and Johns Hopkins Children's Center.

3.2 Allocation to Interventional Group [if applicable]

Following the baseline phase, all subjects will be enrolled in the intervention phase. No randomization or subject group allocation will occur.

3.3 Study Measures

All patients will be enrolled within 24 hours of PICU admission. Using medical records, patient monitoring and environmental monitoring, the following data will be collected for this study.

Baseline and Intervention Phase:

1) Patient comfort will be measured using the following scale, as applicable:
    a. Pain assessed using either the Face, Legs, Activity, Cry, Consolability (FLACC) scale in nonverbal children 0 to 6 years of age, the individualized numeric rating scale (INRS) in nonverbal cognitively impaired children age 6 and older, or the Wong-Baker Faces Pain Scale (WBFPS) in verbal children age 3 and older. All pain scales range 0-10 with higher scores indicating more pain.
    b. Level of sedation in intubated patients is assessed using the State Behavioral Scale (SBS).71 SBS scores range from -3 (unresponsive) to +2 (agitated).
    c. In patients receiving neuromuscular blockade, pain/agitation is judged to be present by the bedside nurse when a patient demonstrates a ≥20% increase in heart rate or blood pressure when stimulated.
    d. Delirium is assessed using either the Cornell Assessment for Pediatric Delirium (CAPD), or the preschool/pediatric CAM instruments; all are rapid bedside screeners for delirium in hospitalized children.
    e. Patients weaning from ≥5 days of sedation are monitored for IWS using the Withdrawal Assessment Tool-1 (WAT-1). The WAT-1 scale ranges 0-12 with higher scores indicating more withdrawal symptoms.
    f. Percentage of total ICU days with no pain, agitation, delirium, or IWS will be monitored and reported.
2) Child's Daily Routine and Sleep Survey – completed at enrollment by a parent
3) Exposure to sedative medications – per medical record
4) The duration of time between the start and stop of all vasoactive medications, from endotracheal intubation to successful endotracheal extubation, from PICU admission to PICU discharge, and from hospital admission to hospital discharge – per medical record
5) Light and noise monitoring - recorded continuously using Quietyme technology
6) EEG, EOG and EMG monitoring for up to 72 hours- EEG will consist of 2 central leads in addition to EOG and EMG (1 lead each on outer corner of the eye and one on the chin).
7) Actigraphy monitoring (placed on wrist or ankle at enrollment) – recorded continuously
8) Saliva Samples – collected with an oral swab eight times across two days (Day 2 & Day 5)
9) Activity Log – completed by parent or nurse daily to record patient activities (such as sleep, feeding, etc)

Intervention Phase:

1) The local investigator(s) or designee will round separately on each enrolled subject daily and complete the R2 bundle adherence form
2) Child's Daily Routine and Sleep Survey – completed at enrollment by a parent
3) The provision of cycled day-night lighted and modulation of sound to match the child's routine (provided by the parent)
4) Minimum but effective sedation administered per RESTORE process – per medical records

5) Night fasting with bolus enteral daytime feedings per child's routine feeding schedule (unless contraindicated) – per medical records and activity log
6) Documentation of one of three physical activities within the PICU Up! program implemented
7) The number of nurses assigned to care for the subject – per activity log
8) Parent diary entries – paper or electronic

Within 48 hours of patient PICU discharge; specifically, after transfer to an inpatient unit:

- Parents will be contacted to complete the Family-Centered Care Scale (FCCS)
    - Completed in person if still hospitalized or over the phone or electronically (using a REDCap database)
    - A 7-item measure of parents' experiences with nursing care and perceptions of being well-cared for during a PICU stay

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The study endpoint will be PICU discharge or PICU day 28, whichever occurs first.

4 Study Population and Duration of Participation

The target population for this study is pediatric patients admitted to the PICU between the ages of 6 months and 18 years who are intubated and mechanically ventilated for acute airways or parenchymal disease, and are expected to be intubated for more than 24 hours.

4.1 Duration of Study Participation

Subject participation will last until PICU discharge or Day 28, whichever occurs first.

4.2 Total Number of Subjects and Sites

No subjects will be enrolled at Penn. Two sites, Children's hospital of Philadelphia and Johns Hopkins Children's Center, will each enroll 30 subjects who provide full usable data (10 baseline/control and 20 intervention).

4.3 Inclusion Criteria

The following is a list of study inclusion criteria:

- PICU admission at one of the study sites in which elements of R2 are typically but sporadically implemented
- Transferred to the PICU from another hospital unit/ward with ≤4 nights in the hospital (≤2 nights in PICU)
- Between the ages 6 months and 18 years at the time of enrollment (has not had their 18th birthday)
- Intubated and mechanically ventilated for acute airway or parenchymal disease within last 48 hours
- Expected to be intubated for more than 12 hours past enrollment
- Parent/Guardian providing consent, provides primary care for subject

4.4 Exclusion Criteria

The following is a list of exclusionary criteria for this study:

- A baseline cognitive dysfunction, measured by the Pediatric Cerebral Performance Category (PCPC ≥4)
- A history of an uncontrolled seizure disorder (seizure within past 3 months), cerebral hypertension, neuromuscular respiratory failure, ventilator dependence (excluding BiPAP or CPAP at night)
- A history of inability to tolerate bolus enteral feeds (full J-Tube fed patients)

- The presence of any of the following within 24 hours of admission:
    - Modal pain scores greater than 4
    - Persistent hypotension/hypertension unresponsive to standard therapies
    - Use of High Frequency Oscillatory Ventilation or Extracorporeal Membrane Oxygenation
- Administered melatonin within the past week
- Has an active do-not-resuscitate plan

4.5 Subject Recruitment

Subjects for this study will be recruited via daily PICU admission logs. Consecutive patients admitted to the PICU at each of the study sites will be reviewed for eligibility (based on medical record) and if eligible invited to participate. After verifying the patient's eligibility status, the patient's legal guardian or parent(s) will be introduced to the research team by a member of the patients care team and informed consent will be requested from the parent or legal guardian. Recruitment will end when 60 subjects are enrolled.

4.6 Vulnerable Populations:

This study involves children. At the time of enrollment, the patient's legal guardian/parents will be introduced to the research team by a member of the patient's care team and informed consent will be requested from the parent or legal guardian. Due to existing medical conditions (e.g. sedation, mechanical ventilation) minor assent will not be obtained. Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania or other involved institutions will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

5 Study Procedures

Following informed consent, during the baseline phase, all patient care will be managed at the discretion of the clinical care team. The study will not provide care recommendations or changes to treatment during the baseline phase.

The following procedures will occur daily during the Baseline and Intervention Phases:

- Completion of the Child's Daily Routine and Sleep Survey
- Patient Activity Log completed by parent or nurse
- Light and noise monitoring within the patient room using Quietyme technology
- Patient EEG monitoring (4 leads) for first 72 hours following enrollment
- Patient actigraphy monitoring (placed on wrist or ankle)

The following activity will occur twice during the study - on Day 2 and Day 5

1) Saliva Samples – an oral swab will be collected a total of eight times per day/2 days (16 total)
    a. A small cotton swab (Salimetrics, Inc, PA) will be placed under the child's tongue for 60-90 seconds then inserted into a storage tube

In addition to those listed above, the following procedures will only occur during the Intervention Phase:

- Use the Child's Daily Routine and Sleep survey data to replicate the child's pre-hospitalization daily routine (bedtime/wake time, bedtime/arousal routine, nap time, feeding schedule, active periods) modulate the PICU environment and child activity
- Window shades and ambient lighting will be modified to provide day/night cycling per child's routine
- Light and sound will be modified throughout the day to match the child's preference and parent reporting

- Sedation managed per RESTORE principles within the PICU's standard of care.
- Enteral feeding will be provided during the day according to the child's routine
- Physical therapy and progressive mobility/exercise will be implemented per the PICU Up! program
- The PICU charge nurse will limit the number of nurses assigned to care for the subject
- Parents will be asked to complete daily diary entries via paper or electronic format

5.1 Screening

Screening activities will take place daily at 10am +/- 2 H for this study. The research coordinator will review the medical records of all PICU admissions within the past 24 hours for demographic and clinical condition to determine initial eligibility. The research coordinator will confirm each potential patient's eligibility with the patient's care team and attending physician. Upon confirmation of eligibility the clinical team will introduce the patient's parent/legal guardian to the study and the research coordinator. For parents/legal guardians interested in participation, informed consent will be obtained.

The following table provides a review of the data collection timeline for this study:

Measurement	Screening	Day 1	Day 2 & Day 5	Daily	PICU Discharge
Demographic Data	X	X			
PCPC/POPC score	X	X			
Medical History	X	X			
PRISM III		X			
Child's Daily Routine and Sleep Survey		X			
Salivary Swab			X		
Ventilation Status, sedative medications, neuromuscular blockades, extubation readiness test				X	
Pain, Sedation, Delirium Scores				X	
WAT-1 Iatrogenic Withdrawal Syndrome assessment				Weaning phase	
Enteral nutrition pattern/volume				X	
Occupational/Physical/Child life therapy				X	
Sound/Light monitoring				X	
EEG monitoring				X (3 days)	
Ankle/wrist Actigraphy				X	
Activity Log				X	
Parent Diary				X	
Family Centered Care Scale (FCCS)					X

5.1.1 End of Study Visit

None required

5.2 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or

study procedures or visit schedules, AEs, or due to a change in medical history (e.g. develop an exclusionary medical condition or medication). The Investigator may also withdraw subjects who violate the study plan, to protect the subject for reasons related to safety or for administrative reasons. It will be documented whether or not each subject completes the study. Subjects who withdraw early will have one final visit to collect final evaluations and assess adverse events.

5.2.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final study visit. During this visit they will be asked for permission to assess their survival status via medical records.

6 Statistical Plan

The study design will allow multiple comparisons; specifically baseline to intervention group and cross-unit comparisons. The specific aim of the study is to pilot test ***RESTORE* resilience**, an individualized chronotherapeutic bundle, in pediatric patients supported on mechanical ventilation for acute respiratory failure in the PICU. The study design is a two-phase prospective cohort study. Subjects will be consecutively enrolled into the Baseline Phase and then into the Intervention Phase in two separate PICUs. Each unit will enroll 10 baseline subjects followed by 20 intervention subjects (total: 20 baseline subjects and 40 intervention subjects). Outcome variables are designed to be as objective as possible since it is not possible to blind the assessor to treatment phase.

6.1 Sample Size and Power Determination

This study is not powered for effect. As a pilot study we are only interested in evaluating the feasibility of implementing all elements of the RESTORE-resilience intervention (see below).

6.2 Statistical Methods

For purposes of this pilot study, we assume that subjects managed per R2 will exhibit maintain circadian rhythmicity and demonstrate an improved sleep-wake pattern, as evidenced by increased circadian activity ratio (daytime activity/total 24-hr activity) post-extubation, compared to those managed per usual care. Preliminary data from current studies in the PICU suggest that 50% of activity occurs during the nighttime hours in the PICU. We anticipate that the R2 intervention will result in a decrease in nighttime activity to 30% of total activity. **This pilot study is exploratory to determine preliminary estimates in order to develop power calculations for a future trial.**

6.3 Control of Bias and Confounding

To avoid bias all eligible subjects will be consecutively approached for consent and we will use objective biological endpoints.

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

Analysis of the primary outcome: Average circadian activity ratio, defined as daytime activity/total 24-hr activity, after extubation as demonstrated by actigraphy. Daytime will be defined as 7 am -7 pm. Validated in infants and children, actigraphs capture activity counts in 1-minute epochs which can be compared between daytime and nighttime hours as a marker of circadian rhythm. Because activity levels vary between patients (i.e., a child with cerebral palsy and/or muscle weakness will not produce the same activity amplitude as a healthy child), the circadian activity ratio provides a method of normalizing the data to account for each patient's baseline amplitude. Increases in the daily circadian activity ratio would suggest improvement in day-night rest-activity patterns and sleep consolidation over time.

7 Safety and Adverse Events

All enrolled subjects are critically ill and no additional study-related risk is anticipated. This section provides the safety management plans for the study if one were to occur. The MPIs will be responsible for ensuring the safety of participants on a daily basis. The MPI and the study coordinators will meet bi-weekly to review current status of the protocol. The bi-weekly meetings will assess the safety of the patients enrolled on the study.

7.1 Definitions

7.1.1 Adverse Event

Patients will be monitored for the occurrence of events defined as any undesirable experience or unanticipated benefit. Patients will be monitored daily to determine whether an event has occurred. All adverse events will be recorded on an adverse event case report form. Serious adverse events (death, life threatening, new serious or permanent disability) will be reported within 24 hours to the MPI team within 72 hours to the Institutional Review Board (IRB). Recommended protocol modifications will be implemented immediately. A description of all undesirable experiences or unanticipated benefits will be recorded on the case report form. In addition, the required interventions, patient's condition after the event, an estimate of the extent of injury, and prevention strategies will be reported. The relationship of the study protocol to the event will be classified by a consensus of the bedside team as follows:

- Not related: The event is clearly related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
- Remote: The event was most likely related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
- Possible: The event follows a reasonable temporal sequence from the implementation of the protocol and/or is consistent with known events related to the protocol but is possibly related to factors such as the subject's clinical state.
- Probable: The event follows a reasonable temporal sequence from the implementation of the protocol and/or is consistent with known events related to the protocol and cannot be reasonably explained by factors such as the subject's clinical state.
- Highly Probable: The event follows a reasonable temporal sequence from the implementation of the protocol and/or is consistent with known events related to the implementation of the protocol and cannot be reasonably explained by factors such as the subject's clinical state. In addition, the event occurs immediately following the implementation of the protocol, or improves when discontinuing the protocol, or reappears on the repeat implementation of the protocol.

7.1.2 Serious Adverse Event

The severity of an adverse event in both phases is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by a consensus of the bedside team as follows:

- Mild: Does not impact (in anyway) the patient's course of illness.
- Moderate: Impacts the subject's course of illness but is not life-threatening or incapacitating.
- Severe: Fatal, life threatening, permanently disabling; severely incapacitating; requires/prolongs inpatient hospitalization.

The principal investigators will immediately follow-up on all serious events on a case-by-case basis. All adverse events will be summarized and reviewed on a monthly basis.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the CRF.

All adverse events occurring during the study period will be recorded. All study related SAE's will be reported to the IRB in writing by the MPI within 24 hours of the event. The following guidelines will be followed: 1) A letter will summarize any adverse events or events that occurred, the patient's name will not be included. The event outcome will be described. 2) An original and 3 sets of documents including the letter, any communication from the study team, and all supporting documents will be provided. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

Following discussion with the attending physician and clinical care team, review of the medical records and any applicable CRFs, the PI will determine the relationship and classification of all AEs.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed within HS-ERA within 10 working days.

All adverse events that are previously undescribed, or serious and study-related are subject to expedited reporting. The NIH will be notified (by telephone, fax, or writing) as soon as possible but no later than 7 calendar days after first knowledge by investigator that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. The NIH report will include:

- Patient details: initials, subject number, gender, age and/or DOB, weight, and height.
- Intervention that resulted in AE or SAE
- Other treatments (same as above) for all other concomitant medicinal products.
- Details of the SAE: description of the event (signs and symptoms/diagnosis); why this is considered serious (criteria); onset and duration of the event; dechallenge/ rechallenge information; setting.
- Outcome: information on recovery and any sequelae; specific treatments/tests and results; cause of death; autopsy or post mortem reports.
- Reporter - name, profession, address, and phone number.
- Determinants of causality - temporal (time) association, known AEs, subject's current state of health, response to dosage change, concomitant medications, other therapies the subject is undergoing.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator’s assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB.

7.4.2 Data and Safety Monitoring Plan

A DSMB will not be required for this study. The PI will monitor this study. Local investigators will contact Dr. Curley immediately, should any unanticipated problems occur. Patients will be monitored for the occurrence of events defined as any undesirable experience or unanticipated benefit. Patients will be monitored daily to determine whether an event has occurred.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The parental permission form for this study informs the parent/subject of the following:

- What protected health information (PHI) will be collected in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PH.

After providing informed consent/parental permission/assent, the subject will be assigned a unique case number. This number will be used to label all private research information, including clinical assessments and saliva swabs. Original signed informed consent forms will be kept in a locked cabinet in a private office. All data and photographs will be entered directly into a password-protected database that will be maintained on a password-protected network drive. Access to the server is through a password-protected account that allows access to data collected only to the investigator and their designees. Consent logs and other research records will be kept for 7 years after the primary paper is published for audit purposes. At that time, they may be destroyed under the direction of the Principal Investigator. Results will only be reported in aggregate form.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Data Collection and Management

The Data Coordinating Center (DCC) will work with the MPI team to develop a web-based Data Management System (DMS) using the REDCap electronic data capture system. According to programmed workflow logic, the DMS will generate electronic Case Report Forms as needed for each patient (e.g., daily forms, study discharge form). The DMS allows for the data to be viewed in real time by the DCC staff and certified data entry personnel at the clinical sites. Many automated logic and range checks and cross-form validations will be programmed to ensure data quality, and audit trails will be maintained.

The DCC will work with each clinical center to ensure that database training and certification is obtained by all new staff and that data are entered, data queries are resolved, and data-related questions are answered promptly.

The DCC will transfer electronic data files as needed in a secure and confidential manner. The DCC will also create reports as needed by the NIH, for study quality review (e.g., monthly protocol adherence reports), and for review as needed by our Data and Safety Monitoring Plan.

Confidentiality will be maintained throughout the study in the following ways:

1) All data will be de-identified then stored in the secure REDCap database or in the Excel database, as appropriate.
2) Specimens will be de-identified and stored in lockable research freezers, and each participant will be assigned a unique identification number.
3) A master list (linking PHI to study ID) will be housed separately from all data forms (both paper and electronically). The master list will be maintained by the PI and stored in a password protected file within Excel on computers on accessible by the study team and password protected.

8.3 Records Retention

Study records will be retained per applicable NIH and Penn IRB requirements. Records will be stored in locked cabinets, in locked offices only accessible to the study team.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study MPIs will be responsible for ensuring the ongoing quality and integrity of the research study.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 Ethical Considerations

10.1 Risks

Privacy and Confidentiality: Strict measures will be taken to ensure participant privacy and confidentiality. All data will be de-identified then stored in the secure REDCap database or in the Excel database, as appropriate. Specimens will be de-identified and stored in lockable research freezers, and each participant will be assigned a unique identification number. The master list linking identification numbers to identifying information will be stored separately from the study database. All personally identifiable information will be kept strictly confidential and stored in an encrypted document, on a dedicated research server only accessible by the research team.
Risk associated with EEG and ankle/wrist monitoring includes irritation at the site and will be minimized by scheduled assessments of the sites, and removal of the device if irritation or redness occurs.

The major components of RESTORE are a standard of care in each PICU. The current study is testing the feasibility of implementing the entire 7-item bundle of activities/clinical care within a PICU, it is not testing each item within the bundle. Risk associated with over and /or under sedation will be minimized by hourly assessment of goal SBS attainment with the subject is intubated.

Risks associated with bolus feed included gastro-esophageal reflux and aspiration. However, children who are at risk for reflux and aspiration will be excluded from the study. Children who have clinical signs of aspiration will be removed from study. Reflux precautions including head of bed at 300 will be implemented when appropriate.

Risks from progressive mobility include inadvertent tube/catheter dislodgement. However, these risks are minimized since the care models at both Johns Hopkins and CHOP have incorporated progressive mobility as part of the standard of care, and are well trained with this intervention. Children at high risk for tube and or catheter dislodgment will not participate in this activity.

10.2 Benefits

10.3 Risk Benefit Assessment

No direct benefit from study participation is expected. Participation may result in the improvement in the environment, daily routine and sleep patterns of children during a stay in the PICU. The findings from this study will increase clinical knowledge regarding the care of critically ill children and how best to preserve and/or restore a child's circadian rhythm. The possible benefits of this study outweigh the risks to participation. We expect these results will contribute to education of pediatric health providers, care of all

pediatric patients with acute respiratory failure, and future studies evaluating the effects of environment and care.

10.4 Informed Consent Process / HIPAA Authorization

All parents/legal guardians of the potential subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be approved by the Penn IRB for this study. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The parent/legal guardian, will sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator, or appropriate designee. Potential subjects will review the consent form in detail with the person designated to consent (either PI or CRC) and have the ability to take the consent home for further review.

In the event of a health pandemic we will use telephone consent and obtain an electronic signature on the R2 parental permission form. This will only be used if parents are prevented from accompanying their child in the hospital because of a pandemic. If ever necessary, we would help the site use an existing e-signature software account or create a new one.

Participants will be informed that their participation in all aspects of the proposed study is entirely voluntary, and that they are free to withdraw at any time. The consent process, which will follow an item-by-item reading of the IRB-approved consent form, will include an explanation of the study, its voluntary nature, compensation, and the risks and benefits of participation. Consent forms will be written at no higher than a 6th grade reading level. All participants will be given the opportunity to ask questions and decline participation. Assent cannot be obtained because children of assenting age will be intubated and sedated. The completed consent document will be signed and dated by the individual obtaining consent, and a copy will be provided to the participating family. Signed consent forms will be stored in a locked cabinet. Should participants become intolerant of the study, their participation will be discontinued. Contact information for study PI and the study team will be included on consent forms to allow participants to ask questions or raise concerns about the study at any time. Should any specific concerns arise, the study team would intervene to address problems including, if needed, a change or discontinuation of study procedures. The study team and IRB will be informed of any concerns, and the NIH will be informed of any adverse events associated with the study.

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the US National Institute of Health- National Institute of Child Health and Human Development.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

There are no subject payments or stipends for participation in this study.

12 Publication Plan

A publication committee will be created to oversee study publications, and publication authorship based on the relative contributions of investigators and staff.

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