



Study protocol for a two-center test of a nurse-implemented chronotherapeutic restoring bundle in critically ill children: RESTORE Resilience (R^2)

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ABSTRACT

Often, pediatric intensive care environments are not conducive to healing the sick. Critically ill children experience disruptions in their circadian rhythms, which can contribute to delayed recovery and poor outcomes. We aim to test the hypothesis that children managed via *RESTORE Resilience* (R^2), a nurse-implemented chronotherapeutic bundle, will experience restorative circadian rhythms compared to children receiving usual care. In this two-phased, prospective cohort study, two separate pediatric intensive care units in the United States will enroll a total of 20 baseline subjects followed by 40 intervention subjects, 6 months to less than 18 years of age, requiring invasive mechanical ventilation. During the intervention phase, we will implement the R^2 bundle, which includes: (1) a focused effort to replicate the child's pre-hospitalization daily routine, (2) cycled day-night lighting and sound modulation, (3) minimal yet effective sedation (*RESTORE*), (4) nighttime fasting with bolus enteral daytime feedings, (5) early progressive mobility (*PICU Up!*), (6) continuity in nursing care, and (7) parent diaries. Our primary outcome is circadian activity ratio post-extubation. We hypothesize that children receiving R^2 will experience restored circadian rhythms as evidenced by decreased nighttime activity while in the PICU. Our exploratory outcomes include salivary melatonin levels; electroencephalogram (EEG) slow-wave activity; R^2 feasibility, adherence, and system barriers; levels of patient comfort; exposure to sedative medications; time to physiological stability; and parent perception of being well cared for. This paper describes the design, rationale, and implementation of R^2 .

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Abbreviations: CINC, continuity in nursing care; DARE, daytime activity ratio estimate; DCC, Data Coordinating Center; DMS, data management system; EEG, electroencephalography; FCCS, Family-Centered Care Scale; ICU, intensive care unit; PCPC, Pediatric Cerebral Performance Category; POPC, Pediatric Overall Performance Category; PICU, pediatric intensive care unit; PRISM III-12, Pediatric Risk of Mortality III score from first 12 h in the PICU; WAT-1, Withdrawal Assessment Tool-1.

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1. Introduction

Hospitals should do the sick no harm [1]. That noted, modern-day pediatric intensive care units (PICUs) are not healing milieus. Immediately upon admission to the PICU, the child's daily routine and sleep patterns are replaced by a well-intentioned, but not patient-centered, PICU routine. Requisite intensive care therapies quickly tax the child's capacity to understand the imperative nature of immobilization and instrumentation, leading to the concurrent use of heavy sedation [2–4]. Individual coping is challenged by the chaotic PICU environment devoid of day-night cycled lighting, frequent physical exams (often hourly), and the continuous sound of alarms and unfamiliar voices. Every day, all day, most children are confined to the bed and receive non-physiologic, continuous enteral tube feedings [5]. Although parents are present, they are often stressed, and their usual caregiving roles are altered and limited [4,6,7]. Collectively, these factors tax the young child and overburden their already compromised physiologic state.

We believe that PICU care and environments can be modulated to sustain a child's circadian rhythm, support their physiological resilience, and enhance their capacity to heal. Children with acute respiratory failure, requiring mechanical ventilation are a highly critical group who may require sedation to safely maintain their critical care instrumentation. The completion of the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) clinical trial (NCT00814099; PI: Curley) provides evidence that mechanically ventilated, critically ill children can be safely managed in a more awake state [2]. Pilot work on *PICU Up!* (PI: Kudchadkar), an intervention promoting early and progressive exercise and mobility in critically ill children, supports its safety and feasibility [8]. We hypothesize that more awake, responsive, and active children who receive circadian rhythm-restoring interventions may demonstrate improved outcomes. 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 patients.

The first step in this program of research is to test *RESTORE Resilience* (R^2 , R21 HD093369; MPI: Curley, Kudchadkar, Zuppa), a 7-item individualized chronotherapeutic bundle. We hypothesize that R^2 will restore circadian rhythm in pediatric patients supported on mechanical ventilation for acute respiratory failure. The nurse-implemented chronotherapeutic bundle includes (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) nighttime 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 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.

2. Methods and analysis

Here we describe the methods and considerations for the R^2 Protocol, utilizing the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement as a guideline [9].

2.1. Study overview and design

The study design is a two-phase prospective cohort study. Eligible subjects are consecutively enrolled in the Baseline Phase and then the Intervention Phase. Recruitment and enrollment will occur in two separate PICUs of similar size, organization, and academic affiliation. Each PICU will enroll 10 baseline subjects followed by 20 intervention subjects (total: 20 baseline subjects and 40 intervention subjects). All

patients are followed to PICU discharge or day 28, whichever occurs first. During the Baseline Phase, all care is managed at the discretion of the clinical team and no recommendations are made (i.e., usual care). During the Intervention Phase, subjects will receive the intervention R^2 , a chronotherapeutic bundle (Table 1). The same patient, environmental, and systems data are collected in each phase.

2.2. Patient selection

PICUs are screened every morning for potential subjects. Eligible patients are direct admissions to the PICU and between the ages of 6 months corrected gestational age and 17 years (has not had their 18th birthday). Eligible patients must be intubated and mechanically ventilated for acute airways or parenchymal disease and, upon the judgement of the clinical team, expected to be intubated for more than 24 h. Additionally, eligible patients must have a primary caregiver present (parent or guardian). Children at high risk for baseline sleep disturbances or those in which implementation of R^2 or data collection is not possible are excluded. Detailed inclusion and exclusion criteria are outlined in Table 2.

2.3. Outcomes and study measurements

The circadian activity ratio, also known as the Daytime Activity Ratio Estimate (DARE), after endotracheal extubation is our primary outcome [10–13]. As measured by actigraphy, DARE is defined as daytime activity/total 24-hr activity. Daytime is defined as 7 a.m. to 7 p.m. Since 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), DARE provides a method of normalizing the data to account for each patient's baseline amplitude. Increases in the daily DARE would suggest improvement in day-night rest-activity patterns and sleep consolidation over time.

In addition to our primary outcome, we have several secondary (exploratory) outcomes of interest which are outlined in detail in Table 3. These exploratory outcomes were selected due to their known association with circadian rhythm disruption in the PICU [2,14–16].

Data collection is the same in both the Baseline and Intervention Phases. Fig. 1 presents the study flow diagram while Table 4 outlines the schedules for data collection, instruments to be completed, and samples to be obtained [16–25]. In addition to existing PICU monitoring and data collection, we will also collect continuous environmental (light and sound) and patient monitoring (EEG, actigraphy, salivary melatonin, and activity logs).

2.3.1. Continuous environmental monitoring

Real-time continuous light luminance and sound monitoring will be conducted using Quietyme™. Quietyme is an environmental monitoring and analytics system that uses a combination of sensors and analytics to provide real-time data on light and sound levels. Sensors are plugged into an existing electrical outlet at the head of the bed space (sensor of record) and adjacent hallway(s) and/or common area(s) (control sensors). The sensors have a measurement range for sound of 25–120 dB (dB; A-weighted) and an accuracy of ± 1 dB. Light and sound levels are measured and collected 1,000 times per second, and the data is sent wirelessly to the sensor hub for data collection and analysis. The

Table 1
RESTORE Resilience 7-item nurse-led chronotherapeutic bundle.

1. A focused effort to replicate the child's pre-hospitalization daily routine
2. Cycled day-night lighting and sound modulation
3. Minimal yet effective sedation (*RESTORE*)
4. Nighttime fasting with bolus enteral daytime feedings
5. Early progressive mobility (*PICU Up!*)
6. Continuity in nursing care
7. Parent diaries

Table 2
RESTORE Resilience inclusion and exclusion criteria.

Inclusion Criteria
1. ≥ 6 months corrected gestational age and ≤ 17 years of age
2. ≤ 4 nights in the hospital (≤ 2 nights in the PICU)
3. Intubated and mechanically ventilated for acute airways or parenchymal disease
4. Expected to be intubated for more than 24 h
5. Caregiver (parent or guardian) present who provides primary care for the child
Exclusion Criteria
1. Baseline cognitive dysfunction (PCPC >3)
2. A history of an uncontrolled seizure disorder (seizure within past 3 months)
3. Cerebral hypertension
4. Neuromuscular respiratory failure
5. Ventilator dependence (excluding BiPAP or CPAP at night)
6. History of inability to tolerate bolus enteral feeds
7. Have had any of the following within 24 h of admission: <ul style="list-style-type: none"> - Modal pain scores >4 - Persistent hypotension/hypertension unresponsive to standard therapies - High-Frequency Oscillatory Ventilation - Extracorporeal Membrane Oxygenation
8. Prescribed melatonin in the last week
9. Active do-not-resuscitate plans

Table 3
Primary and secondary endpoints.

Endpoint	Measurement
<i>Primary Outcome</i>	
Circadian activity ratio (DARE) after endotracheal extubation ^a	Daytime activity/total 24-h activity assessed by actigraphy.
<i>Secondary Outcomes</i>	
Salivary melatonin levels	On days two and five, a small cotton swab (Salimetrics, Inc, PA) is placed under the child's tongue for 60–90 s then inserted into a storage tube. The tubes are immediately centrifuged for 15 min at 3500 rpm to extract the saliva, and frozen at -40 °C. The saliva samples are thawed, centrifuged, and pipetted into wells. We will use a competitive enzyme immunoassay (Salimetrics, Inc.) to quantify salivary melatonin per standard protocols.
Nighttime EEG slow-wave activity during endotracheal intubation	2-lead continuous EEG monitoring (C4-M1) begins at the time of enrollment and continues for up to 72 h.
R ² feasibility, adherence, system barriers	During the Intervention Phase, the local investigators or designee will round separately on each enrolled subject each day and offer staff support and retraining as necessary.
Levels of patient comfort	PICU days free of pain, agitation, delirium, and iatrogenic withdrawal.
PICU exposure to sedative medications	Total dose and length of exposure. All sedatives administered in the PICU are extracted from existing documentation and analyzed as previously described per RESTORE.
Time to physiological stability	Time on vasoactive medication, duration of mechanical ventilation, PICU and hospital length of stay. 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 are extracted from existing documentation.
Parent perception of being well-cared for	Within 48 h of PICU discharge, the consenting parent or guardian is asked to complete the Family-Centered Care Scale, a 7-item valid and reliable measure of parents' experiences of nursing care that embodies core principles of family-centered care.

^a Primary endpoint.

continuous light and sound levels (1,000 time per second) are aggregated by Quietyme and are subsequently reported in 60-min segments as minimum, mean, and maximum values. Hourly data will then be organized into daytime (7 a.m.-7 pm) and nighttime (7 p.m.-7 am) categories.

2.3.2. Patient monitoring

Each enrolled child will have a portable, two-lead electroencephalography (EEG) monitoring device and actigraph applied. EEG leads (Avatar EEG, Philips Inc.) are placed to monitor C4-M1 recordings and initiated by 7 p.m. on the day of enrollment. Initiation by 7 p.m. will ensure ultradian and circadian alterations in sleep are comparable across subjects. The EEG leads will remain in place for up to 72 h.

The actigraph (Micro Motionlogger®, Ambulatory Monitoring, Inc.) is placed on an unrestrained wrist or ankle and will remain until PICU discharge. Wrist or ankle placement is selected based on the bedside nurse's clinical judgement (i.e. inaccessible limb related to peripheral line placement), patient age and/or parent/guardian preference. [26] Validated in infants and children, actigraphs capture activity counts in 1-min epochs which can be compared between daytime and nighttime hours as a marker of the circadian rhythm. A bedside log is used to document any reasons for actigraph removal, and a member of the study team will monitor the watch daily for any evidence of skin breakdown, irritation, or device malfunction. The actigraph remains in place from study enrollment to PICU discharge unless child has evidence of the aforementioned complications as documented in the daily log.

Saliva samples for salivary melatonin are collected from all subjects on days two and five. Melatonin is serially collected every 3 h for a 24 h period (between 7 a.m. and 7 a.m.).

Existing PICU nursing documentation includes child feeding, hygiene, pain/agitation/delirium scoring, comfort medication, and neuromuscular blockade. Bedside activity logs are placed at each bedside to supplement existing nursing documentation. The supplemental activity logs include documentation not generally captured by the bedside nurse, including wake time/naps/bedtime, physical activity, diversional activity, child life therapy, planned quiet time, and parent presence. Similar to sleep logs, these activity logs serve as a proxy in a population who is unable to self-report in an effort to enhance the validity of actigraph data [27]. The logs are completed by the bedside nurse daily and, if interested, parents may enter log entries.

2.3.3. Patient and public involvement

Parents actively participated in developing the Children's Daily Routine and Sleep Survey. The pilot-test of the survey was met with great enthusiasm from parents. A majority of parents (87%) rated the level of burden less than 2 on a 10-point Likert scale (median, 0) [28]. In addition, the parents of enrolled children are active participants in the implementation of R².

2.4. Study phases

2.4.1. Baseline phase: usual care

Each PICU will continue their usual standard of care during the Baseline Phase. Data is collected with no change in the standard management of mechanically ventilated children and/or environmental modification.

2.4.2. Intervention phase: chronotherapeutic bundle (RESTORE Resilience)

Within the Intervention Phase, all data elements above are collected with the implementation of the following individualized, 7-item chronotherapeutic bundle. The components of the bundle are as follows:

- 1) As soon as possible after PICU admission and enrollment, when emotionally accessible, consenting primary caregivers (parent or guardians) are asked to complete the **Child's Daily Routine and Sleep Survey** (Appendix A) with the assistance of the bedside nurse.

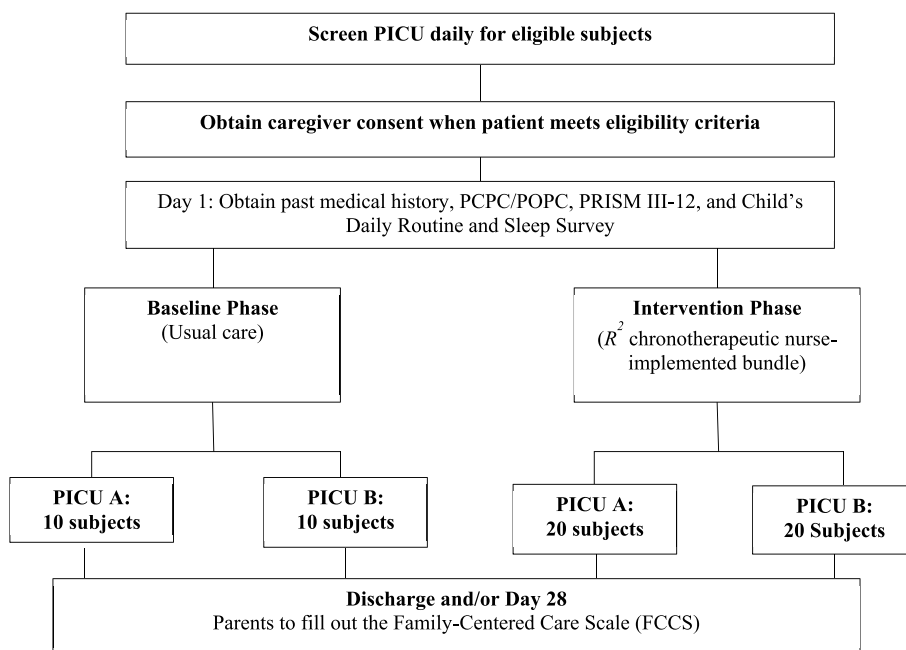


Fig. 1. RESTORE Resilience study flow diagram.

The completed survey will then be used as a template for the subject's daily schedule while in the PICU; specifically, feeding schedules/eating, wake time/naps/bedtime, hygiene, daytime activities (physical activity/play, computer/TV), and bedtime/arousal routine. The daily schedule is posted in the child's room in clear sight. Primary caregivers are specifically invited to partner with their child's nurse in helping to create a familiar environment/routine for their child. Modifications in the daily schedule will incorporate feedback from the child's interprofessional team including the PICU physician, nurse practitioner, respiratory therapist, clinical pharmacist, nutritionist, physical/occupational therapist, and child life therapist.

- 2) **Cycled day-night lighting and modulation of sound** is provided to match the child's routine. Window shades and ambient lighting are modified to provide day-night cycling. Light and sound are modified throughout the day to match the child's preferences.
- 3) The subject's sedation is managed per **nurse-implemented, goal-directed sedation**. Core elements include daily team discussion of the patient's trajectory of illness (acute, titration, or weaning phase)

during daily interprofessional rounds; prescribing a sedation target score per phase of illness; modified arousal assessment if responsive only to noxious stimuli or full arousal assessment if unresponsive to stimulation in the titration/weaning phases; daily extubation readiness test; adjustment of sedatives based on the phase of illness at least every 8 h; and discontinuation of opioids and benzodiazepines when no longer necessary.

- 4) **Nighttime fasting with bolus enteral daytime feedings** is administered, unless contraindicated, per the child's routine feeding schedule. The child's daily caloric and volume requirements are administered from 8 a.m. through as late as 10 p.m. on an intermittent bolus schedule. This approach is determined upon consultation and agreement between the PICU's nutritional consultant and the primary clinical team.
- 5) **Physical therapy and progressive mobility and/or exercise** are implemented as outlined in the structured tiered *PICU Up!* Program [8]. In *PICU Up!* one of three levels of physical activity, stratified by the child's severity of illness, is prescribed and then reviewed daily during interprofessional rounds. Each level is associated with

Table 4
RESTORE Resilience instruments and timeline.

Measurement	Screening	Baseline	Daily	Day 2 & 5	PICU Discharge
Demographic information	X	X			
Medical history	X	X			
PCPC/POPC score	X	X			
PRISM III-12 score		X			
Child's Daily Routine and Sleep Survey		X			
Salivary swab (collected every 3 h)				X	
Ankle/wrist actigraphy			X		
EEG monitoring for <72H while intubated			X		
Sound and light monitoring			X		
Ventilation status, sedative medications, neuromuscular blockade, extubation readiness test			X		
Pain, sedation, delirium scores			X		
Iatrogenic withdrawal syndrome assessment/WAT-1 score					Weaning phase
Enteral nutrition pattern/volume			X		
Occupational/Physical/Child life therapy			X		
Activity Log			X		
Parent Diary			X		
Family-Centered Care Scale (FCCS)					X

age-based, developmentally appropriate activities with criteria to pause and reassess the child's activity based on changes in vital signs, mental status, or concerns about device integrity.

- 6) The child's **continuity in nursing care** (CINC) is managed by the PICU charge nurse(s); specifically, the charge nurses will work to limit the number of different bedside nurses assigned to care for subjects.
- 7) Parents are coached to consider using a paper or electronic **diary** to track their PICU stay. Daily diary sections include the day's events, thoughts, and questions to ask the care team.

2.5. Interprofessional team training

Team training will include just-in-time training of all clinicians involved in the clinical management of enrolled subjects. A multidisciplinary, cooperative approach is necessary to assure adherence and successful implementation of the R² protocol. Web-based *RESTORE* and *PICU Up!* training materials are augmented to include discipline-specific lectures, informal discussions, bedside booklets, and order templates to support R². Each of the two sites have previously participated in *RESTORE* and/or *PICU Up!* [8,29] As such, additional training is focused on reinforcement of bundle aspects, which may not routinely be utilized in each respective PICU. Nursing education will focus on environmental monitoring and implementation of chronotherapeutic interventions. Parents are welcomed participants in their child's care.

2.6. Data coordinating center

The Data Coordinating Center (DCC) will work with the team to develop a web-based Data Management System (DMS) using the InForm electronic database capture system (Oracle Health Sciences, Redwood Shores, CA). 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 clinical sites. Many automated logic and range checks and cross-form validations are programmed to ensure data quality, and audit trails are 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 transfers electronic data files as needed in a secure and confidential manner. The DCC also creates reports as needed by the National Institutes of Health, for study quality review (e.g., monthly enrollment and protocol adherence reports), and for review as needed according to our Data and Safety Monitoring Plan.

2.7. Statistical considerations

The study design will allow several comparisons, including Baseline to Intervention Phase and cross-unit comparisons. To avoid bias, outcome variables in R² are biological endpoints designed to be as objective as possible since it is not possible to blind the assessor to the treatment phase.

2.7.1. Sample size

We assume that patients managed per R² will exhibit and maintain circadian rhythmicity and demonstrate an improved sleep-wake pattern, as evidenced by increased DARE post-extubation, compared to those managed per usual care. Practice patterns 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 study is exploratory and is not powered for effect. However, 20 Baseline Phase and 40 Intervention Phase subjects should be sufficient to determine preliminary effect size and variability estimates to develop power calculations for a future trial.

2.7.2. Statistical analysis plan

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 DARE 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 (including linear, logistic, and proportional hazards regression) will be used to assess the effects of covariates on secondary outcomes. Though we do not anticipate differences due to sex/gender, race/ethnicity, or PICU, we will assess the main effects and possible effect modification due to these factors using regression methods. Data analyses will be performed using SAS® (Version 9.4, SAS Institute, Inc., Cary, NC) or similar statistical packages.

3. Ethics and dissemination

3.1. Ethical considerations

This study includes the recruitment and enrollment of critically ill children requiring mechanical ventilation for acute lung disease. Each PICU received approval from their respective Institutional Review Boards. The study itself presents minimal risk, which is outweighed by the potential benefits. Potential benefits to subjects enrolled during the Intervention Phase include improved sleep-wake patterns, improved levels of patient comfort, decreased total sedative exposure, shorter time to physiological stability, reduced PICU and hospital length of stay, and improved parent perception of being well-cared-for.

After verifying the potential subject's eligibility, the primary caregiver (parent or legal guardian) is introduced to the research staff by a member of the patient's care team. Informed consent is obtained from the parent or legal guardian. Parental/guardian informed consent is obtained upon enrollment. Parent/guardians are made aware that they are free to withdraw their consent at any time. While it is unlikely due to the intensive care therapies provided, child assent will be obtained when feasible; specifically, in children ≥8 years of age who have not received sedation for ≥3 days.

In addition to ethical approval by the appropriate Institutional Review Boards, this study has been externally peer reviewed and evaluated competitively by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NIH) [R21HD093369].

3.2. Dissemination

This timely work will be disseminated through various methods to ensure that it is widely available to the general public and key stakeholders, including healthcare providers and the parent/guardians of critically ill children themselves. Findings from R² will be shared and data deposited appropriately as required by the NIH Data Sharing Policy (grants.nih.gov/grants/policy/data_sharing/index.htm title="https://grants.nih.gov/grants/policy/data_sharing/index.htm">https://grants.nih.gov/grants/policy/data_sharing/index.htm). Additionally, we aim to publish results in accessible high-impact, peer-reviewed journals and public forums (i.e. scientific presentations, social media) to ensure visibility to key stakeholders. All this will be done to create lasting change in the management of critically ill children's circadian rhythms, to restore resilience.

4. Discussion

Each year, more than 250,000 infants and children in the United States receive PICU care, and more than 100,000 are supported on mechanical ventilation [30]. With improved mortality, the focus of PICU care has shifted to patient and family morbidity and improvement in quality of life [31–33]. As such, the implementation of R², a chronotherapeutic nurse-led bundle, in the PICU is a necessary first step to decrease incidence of morbidity and improve a child and family's overall quality of life. In adults, we know that disruptions in circadian rhythm may impair mentation, immunity, autonomic function, endocrine activity, hormonal signaling, and ultimately healing [34–37]. As acuity of illness increases, circadian rhythmicity may be eliminated. Causes of circadian disruption may be environmental or internal to the patient [38]. For example, inadequate daytime illumination and increases in nocturnal light, coupled with sudden and frequent peaks in sound with high baseline sound levels and immobility, negatively impact both sleep onset and sleep continuity in the intensive care unit (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 [34,38–45]. In pediatrics, sleep recommendations are age-based and reflect neurologic maturation [46–50]. 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 [14,46,51,52]. 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 [53]. Without data on the physical and psychological benefits of sleep in critically ill children, long-established hospital routines will continue to disrupt their circadian rhythms. This is why we propose a test of an individualized, chronotherapeutic bundle to mitigate circadian rhythm disruption and provide evidence to support sleep enhancement in the PICU — R². The following will outline the importance of each component of the bundle and why it is vital to promote recovery in the PICU.

4.1. Rationale for chronotherapeutic bundle elements

4.1.1. A focused effort to replicate the child's pre-hospitalization daily routine

Having a child in the PICU is an extremely stressful time for parents and/or guardians. Parent/guardian interviews are the first step in carrying out the chronotherapeutic bundle, as it provides the bedside team with vital information concerning the child's normal routine. This information is the basis for individualization of the bundle. The Child's Daily Routine and Sleep Survey is completed as soon as possible after enrollment. The survey was developed with parent input and shared with the bedside clinical team, most felt that the child's schedule could be easily mirrored within the PICU setting.

4.1.2. Cycled day-night lighting and sound modulation

With the implementation of an individualized plan based on parental input, the PICU can be adequately optimized for healing, especially with the provision of environmental modification, such as light and sound modulation to effectively mimic day-night cycling to maintain circadian rhythm. Specifically, noise pollution is a serious concern for recovery and has been acknowledged for its negative effects as early as the 1800s [1]. In response to the negative effects of sound, the World Health Organization (WHO) put forth standardized guidelines regarding appropriate sound levels in the hospital, recommending that average levels not exceed 35 dB (dB) and a maximum of 40 dB overnight [54]. A recent multi-site study surveyed several PICUs' light and sound levels and identified that average sound levels always exceeded 45 dB, with peaks above 85 dB at all sites [55]. In addition to sound, the absence of

day-night light variation can disrupt diurnal melatonin levels and circadian rhythm. In a preliminary assessment, we compared a standard occupied PICU room with window shades positioned at the discretion of the bedside team to emulate normal conditions, and an office with natural sunlight for 3 days. Not surprisingly, the PICU room had no day-night light variation despite the presence of a window. Observed average light patterns within the PICU were 260 units \pm 7 during the day and 247 units \pm 7 at night. The office with natural sunlight experienced varied light levels, with an average of 5,861 units \pm 11,620 during the day and 78 units \pm 290 at night (unpublished data). Therefore, there is a demonstrated need for environmental modification within PICUs, to promote circadian rhythm maintenance and subsequent healing throughout critical illness.

4.1.3. Minimal yet effective sedation

Another crucial component of our R² intervention is nurse-implemented, goal-driven sedation. We have previously demonstrated within the RESTORE trial that mechanically ventilated children can safely be managed in a more awake state. In RESTORE, 2,449 mechanically ventilated children were managed using either unit-specific standard of care or a nurse-implemented, goal-driven sedation protocol. Children randomized to nurse-implemented, goal-driven sedation experienced fewer days of opioid administration, less sedative exposure, and were awake and calm for a greater percentage of study days. While the use of a goal-directed, nurse-driven sedation protocol did not increase the number of ventilator-free days, it did change the patient's sedation experience with no serious adverse events [2]. This is significant as there is increasing evidence of neurocognitive and structural changes within the brain after administration of opioids and other anesthetics in early childhood [56]. Therefore, minimal yet effective sedation is key to improving a child's PICU experience and long-term trajectory.

4.1.4. Nighttime fasting with bolus enteral daytime feedings

The provision of nutritional support in the PICU is also essential to promote healing [57]. The American Society of Parental and Enteral Nutrition offers guidelines on the support of critically ill children, though acknowledges the lack of research and clinical trials that makes decision making in the PICU challenging [58]. Generally, standards of care in the PICU include combinations of 24-h continuous enteral feeding and/or bolus feeds at prescribed time points. Our protocol aims to normalize the home feeding/eating routine with bolus feeds during the day and nocturnal fasting, as the previously healthy child would do. The benefit of bolus feeds is that they are more physiologically aligned with day-to-day routines and provide the child freedom to move and participate in rehabilitation therapies once stable [59].

4.1.5. Early progressive mobility

This is vital considering that early rehabilitation minimizes PICU-acquired weakness and muscle atrophy and decreases PICU length of stay, all while improving functional outcomes [60,61]. Early rehabilitation and mobilization efforts have been proven to be safe and feasible in critically ill children, yet 20% of PICU patients are completely immobile on any given day [5,62]. Moreover, children with normal baseline function are more likely to have delays in rehabilitation team consultation [62]. To date, PICU Up! has been trialed in more than 2,000 critically ill children (NCT03860168) [63]. While its long-term outcomes have not been systematically explored, these children have remained free from adverse events related to early mobilization. Additionally, bedside providers have expressed their interest in PICU Up!'s implementation, with little difficulty in overall facilitation [8].

4.1.6. Continuity of nursing

To ensure adherence to the bundle's components of environmental modification, nutritional support, and early mobilization, continuity of nursing care is imperative. With overall guidance from the Child Daily

Activity and Sleep Survey, the bedside nurse can adequately modulate the critically ill child's environment to closely match their pre-PICU routine. In providing consecutive days of hands-on care, nurses are well-suited to carry out the R² bundle.

4.1.7. Parent diaries

To further support patients and families, parents and/or guardians are given PICU diaries. PICU diaries have been shown to be beneficial to families and may aid in decreasing anxiety in patients and posttraumatic stress disorder among relatives [64,65]. Conflicting results are present in the adult literature, where it has been reported that while ICU diaries may be beneficial to the patient, it may not directly benefit relatives [66]. We know in pediatrics, however, that the family unit is central to the child's overall well-being [67]. Therefore, there is an appropriate emphasis on family-centered care which we will address through providing PICU diaries that parents and/or guardians can use as they see fit.

4.2. Limitations

We have selected known drivers of circadian rhythm that may be modifiable in the PICU. That noted, unknown drivers are not included. In addition, nuances in the critically ill patient are not considered, for example, the impact of a facial edema and/or closed eyes on retinal stimulation. Finally, we selected critically ill pediatric patients with acute respiratory failure and DARE might be different in other critically ill pediatric populations.

5. Conclusion and clinical implications

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. We aim to implement R² to restore resilience and decrease the associated burden of critical illness in children. Optimizing circadian rhythm 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 [68,69]. Although individual elements of R² are practiced in many PICUs, the R² bundle in its entirety has not been systematically 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, yet pragmatic, approach is needed to optimize the healing milieu in the PICU and characterize the functional changes that occur as a result of disrupted circadian rhythm in PICU survivors. Our team intends to shift the current PICU paradigm from potentially toxic to healing for the most vulnerable of patients.

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Author declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2021.100840>.

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