RESTORE

(**R**andomized **E**valuation of **S**edation **T**itration f**O**r **R**espiratory failur**e**)

Sedation Management in Pediatric Patients with Acute Respiratory Failure

U01 HL086622 and U01 HL086649

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ABSTRACT

Ensuring the safety and comfort of critically ill infants or children supported on mechanical ventilation is integral to the practice of pediatric critical care. (1-3) Humane care of this patient group requires the concomitant use of sedatives; most commonly, various combinations of opioids and benzodiazepines. (2, 3) Although there are clear benefits in using sedation in young patients who are unable to understand the imperative nature of critical care instrumentation and immobility, sedative use is associated with iatrogenic injury. Specifically, the medications used for sedation may depress spontaneous ventilation and prolong the duration of mechanical ventilation. (4-8) Over time, drug tolerance develops and may precipitate iatrogenic withdrawal syndrome when sedation is no longer necessary. (3, 9-11) Prolonging the duration of mechanical ventilation and iatrogenic withdrawal syndrome add to the personal and financial burden of intensive care.

This cluster randomized clinical trial will test an innovative approach to sedation management that includes: [a] team education and consensus on the use of sedatives in pediatric patients supported on mechanical ventilation, [b] team identification of the patient's trajectory of illness and daily prescription of a sedation goal, [c] a Nurse-Implemented Goal-Directed Comfort Algorithm that guides moment-to-moment titration of opioids and benzodiazepines, and [d] team feedback on sedation management performance. The intervention is an organizational change directed at all PICU clinicians. The unit of randomization is the PICU, the unit of inference is the patient, and we will control for center effects. Approximately 26 pediatric intensive care units (approximately half randomized to the pediatric sedation management intervention and the remainder to continue to provide usual care) will enroll 2900 critically-ill infants and children supported on mechanical ventilation. We believe that patients managed per sedation protocol will experience fewer days of mechanical ventilation, less sedative exposure, fewer iatrogenic withdrawal symptoms, a shorter intensive care length of stay, less costs, and experience a better post-discharge quality of life and emotional health. The *RESTORE* trial has been registered with ClinicalTrials.gov (NCT00814099).

PROTOCOL SUMMARY

Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Phase: Phase 3

Funding: U01 HL086622 and U01 HL086649

Committees: Steering Committee, Operations Committee, Ancillary Study Committee, (External) Data and Safety Monitoring Board

Background and significance:
Over 90% of infants and children supported on mechanical ventilation receive some form of sedative therapy, often various combinations of opioids and benzodiazepines. While sedation helps keep patients safe and comfortable, sedation may also prolong the duration of mechanical ventilation adding to the personal and financial burden of intensive care.

Protocol-directed sedation, daily interruption of all sedative infusions (wake-up tests/arousal assessments) and daily extubation readiness tests (ERT) have been associated with shorter durations of mechanical ventilation in adult ICU patients. The proposed pediatric sedation management protocol (*RESTORE*) is intended to balance the risk-benefit ratio of sedation in pediatric patients supported on mechanical ventilation for acute respiratory failure. *RESTORE* models the most recent Society of Critical Care Medicine sedation clinical practice guidelines and addresses the only manipulable factor influencing extubation failure rates in the PICU. Ultimately, confirming the benefit of this intervention will establish a PICU standard of care that will influence clinician education, care of all pediatric patients supported on mechanical ventilation, and future studies evaluating new or different combinations of sedative agents.

Study aims:

1. To conduct a multicenter trial to test whether pediatric patients with acute respiratory failure managed per pediatric sedation management protocol experience fewer days of mechanical ventilation than patients receiving usual care.
2. To describe the feasibility of the pediatric sedation management protocol in regards to financial cost.
3. To compare the post-discharge quality of life and emotional health in pediatric patients managed per pediatric sedation management protocol to those receiving usual care.

Study design: Multicenter cluster randomized clinical trial. The unit of randomization is the PICU; the unit of inference is the patient.

Study population: Critically-ill infants and children supported on mechanical ventilation.

Treatment groups:
All PICUs will provide baseline data for approximately three months during which time they will provide their usual sedation management. The PICUs will then be block randomized by size (small, medium, or large based on previously completed mock-screening tools and organizational assessment forms and on their baseline phase enrollments) and batch (first or second batch) to either the control or the pediatric sedation management protocol/intervention group.

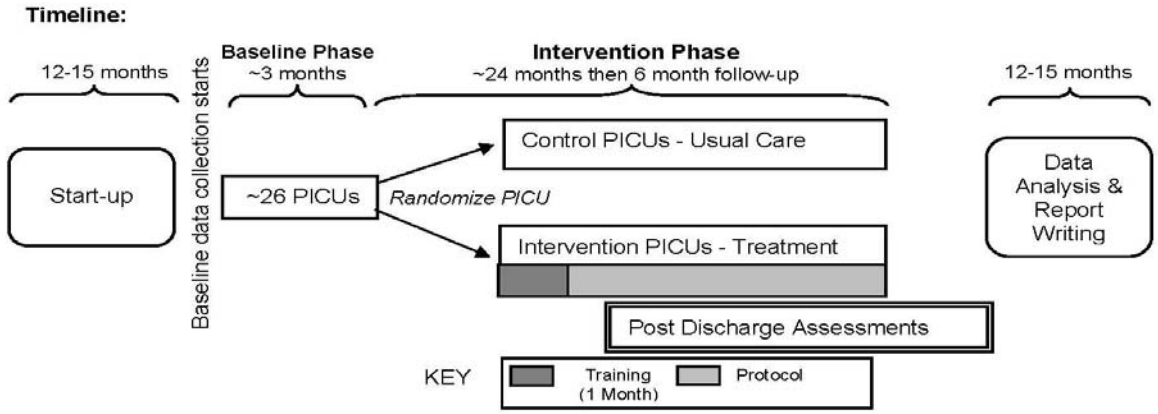
Control PICU: Continue usual care for sedation management.

Treatment PICU: Implement the pediatric sedation management protocol as a research intervention in consented patients. *RESTORE* includes:

- Team education and consensus on the use of sedatives in pediatric patients with respiratory failure supported on mechanical ventilation
- Team identification of the patient's trajectory of illness and daily prescription of a sedation goal
- A Nurse-Implemented Goal-Directed Comfort Algorithm that guides moment-to-moment titration of opioids and benzodiazepines
- Team feedback on sedation management performance.

Patients in both groups will be consented, enrolled and followed within 24 hours of endotracheal intubation to the end of their scheduled sedation therapy, hospital discharge, or Day 28 (whichever comes first). Safety outcomes will be tracked through hospital Day 90.

Half of the subjects enrolled in the trial and their parents/legal guardians will be selected for a telephone-based follow-up interview 6 months after PICU discharge to assess the patient's long-term quality of life, psychologic sequelae, and post-discharge health-related resource use. This sample will be stratified by study site and age (<2 years, 2-4 years, 5-7 years, 8-12 years, and 13-18 years).



Inclusion criteria:

- ≥ 2 weeks of age, ≥ 42 weeks post-menstrual age, and <18 years of age
- Supported on mechanical ventilation for acute lung disease. Lung disease includes both airways and parenchymal disease.

Exclusion criteria:

- Cyanotic heart disease with unrepaired or palliated right to left intracardiac shunt
- History of single ventricle at any stage or repair
- Congenital diaphragmatic hernia or diaphragm paralysis
- Primary pulmonary hypertension
- Critical airway or anatomical obstruction of the lower airway
- Ventilator dependent on PICU admission
- Neuromuscular respiratory failure
- Spinal cord injury above the lumbar region
- Pain managed by patient controlled analgesia or epidural catheter
- Patient transferred from an outside ICU where sedatives had already been administered for more than 24 hours

- Family/medical team has decided not to provide full support
- Enrolled in any other critical care interventional clinical trial concurrently or within the last 30 days
- Known allergy to any of the study medications
- Pregnancy

Study sample size: 2900 subjects from approximately 26 pediatric intensive care units (up to 452 baseline and wash-in phase patients and 1224 patients in each group or 2448 total during the intervention phase).

Endpoints:
Primary:

- Duration of mechanical ventilation (equivalent to ventilator-free days)

Secondary:

- Time to recovery of acute respiratory failure
- Duration of weaning from mechanical ventilation
- Occurrence of adverse events
- Detection of life-threatening neurological events
- Total sedative exposure
- Occurrence of iatrogenic withdrawal symptoms
- PICU and hospital length of stay
- Hospital costs
- Protocol implementation costs and cost-effectiveness
- In-hospital mortality
- Post-discharge quality of life and emotional health

Statistical issues:
Primary hypothesis: Pediatric patients with acute respiratory failure managed per sedation protocol will experience fewer days of mechanical ventilation than patients receiving usual care.

Sample size: The target sample size of 2448 enrolled subjects in the intervention phase yields 90% power to detect a 20% reduction in duration of mechanical ventilation controlling for censoring, three formal interim analyses for early stopping, modest within-site correlations (intra-cluster correlation coefficient (ICC) from two-site pilot sedation management study = 0.01), and moderate site-to-site variability in cluster sizes.

Analysis plan: The primary analysis will compare the duration of mechanical ventilation in intervention vs. control subjects using Kaplan-Meier survival curves and proportional hazards regression (including Lin and Wei's sandwich variance estimator to control for PICU as a cluster variable). The duration of mechanical ventilation will be censored at 28 days for patients still intubated on day 28 or patients who die prior to day 28 and had not remained extubated for >24 hours prior to death. Secondary analyses of the primary outcome will compare duration of mechanical ventilation among survivors and assess the binary outcome of whether or not there was a successful extubation during the first 28 days, treating the non-survivors as failures.

Analyses of secondary endpoints will use proportional hazards regression for time to event outcomes, linear regression for continuous outcomes, and logistic regression for binary outcomes comparing intervention vs. control subjects while controlling for variables that are likely to be associated with outcomes, including severity of illness, age, disease process, and use of chemical paralysis. For non-normal continuous outcomes, data transformations or nonparametric methods will be considered, as appropriate. Through all analyses, generalized estimating equations or mixed effects models will be used to control for PICU as a cluster variable.

Monitoring: The study will include three formal interim analyses for early stopping after approximately 400, 1200, and 1800 subjects have their outcomes collected. There will also be review of study endpoints and adverse events by the Data and Safety Monitoring Board at these times, or as requested by the Data and Safety Monitoring Board.

Estimated timeline:
Baseline phase: Approximately 3 months
Training: Approximately 2 months
Intervention phase: Approximately 36 months
Post-discharge assessments: Approximately 36 months
Funding ends 3/31/2013

ABBREVIATIONS

AACN	American Association of Critical Care Nurses
AAP	Assume Agitation Present
AIR	Assessment-Intervention-Reassessment
ALI	Acute Lung Injury
ANOVA	Analysis of Variance
APP	Assume Pain Present
ARDS	Acute Respiratory Distress Syndrome
ASHP	American Society of Health-Systems Pharmacists
ATS	American Thoracic Society
BiPAP	Bi-level Positive Airway Pressure
CA-BSI	Catheter-Associated Blood Stream Infection
CCM	Critical Care Medicine
CHB	Children's Hospital Boston
CHWisc	Children's Hospital Wisconsin
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CNMC	Children's National Medical Center
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRISMA	Clinical Research, Investigation, and Systems Modeling of Acute Illness Center
DCC	Data Coordinating Center
DCF	Data Collection Form
DMS	Data Management System
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
ED	Emergency Department
ERT	Extubation Readiness Test
ESPNIC	European Society of Pediatric and Neonatal Intensive Care
ETT	Endotracheal Tube
FLACC	Facial expression, Leg movement, Activity, Cry, and Consolability
GCS	Glasgow Coma Scale
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICC	Intra-cluster Correlation Coefficient
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ISD	Information Services Department
IHI	Institute for Healthcare Improvement
IMV	Intermittent Mandatory Ventilation
INRS	Individualized Numeric Rating Scale
IQR	Inter-Quartile Range
IRB	Institutional Review Board
ITQOL	Infant Toddler Quality of Life Questionnaire
LOS	Length of Stay
MAAS	Motor Activity Assessment Scale
MMAAS	Modified Motor Activity Assessment Scale
MOO	Manual of Operations

MOOP	Manual of Operations and Procedures
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NNIS	National Nosocomial Infections Surveillance System
NRS	Numeric Rating Scale
PALISI	Pediatric Acute Lung Injury and Sepsis Investigator Network
PCA	Patient Controlled Analgesia
PCEHM	Panel on Cost and Effectiveness in Health and Medicine
PCPC	Pediatric Cerebral Performance Category
PD	Protocol Deviation
PedsQL	Pediatric Quality of Life Inventory
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
POPC	Pediatric Overall Performance Category
PRISM III	Pediatric Risk of Mortality III
PRN	*Pro re nata* (as needed)
PS	Pressure Support
PTSD	Post-Traumatic Stress Disorder
QALY	Quality-Adjusted Life Years
QI	Quality Improvement
RASS	Richmond Agitation-Sedation Scale
SAE	Serious Adverse Event
SAS	Sedation-Agitation Scale
SBS	State Behavioral State
SOP	Standard Operating Procedures
VAP	Ventilator Associated Pneumonia
WAT	Withdrawal Assessment Tool
WAT-1	Withdrawal Assessment Tool - Version 1

A. SPECIFIC AIMS

Over 90% of infants and children supported on mechanical ventilation receive some form of sedative therapy; most commonly, various combinations of opioids and benzodiazepines. (2, 3) Sedation in this patient population is required for anxiolysis, facilitation of care, and patient safety. (12) Although there are clear benefits in using sedation in pediatric patients who are unable to understand the imperative nature of critical care instrumentation and immobility, (1, 6) sedative use is associated with iatrogenic injury. Specifically, the medications used for sedation may depress spontaneous ventilation and prolong the duration of mechanical ventilation leading to an increased risk of pneumonia and other complications. (4, 5, 7, 8, 13) Over time, drug tolerance develops and may precipitate iatrogenic withdrawal syndrome when the sedative agents are no longer necessary. (3, 9-11) Prolonging the duration of mechanical ventilation and iatrogenic withdrawal syndrome adds to the personal and financial burden of intensive care.

We have completed a three-year pilot study testing a protocol intended to balance the risk-benefit ratio of sedation in pediatric patients supported on mechanical ventilation for acute respiratory failure in the Pediatric Intensive Care Unit (PICU) [R21HD045020]. This pediatric sedation management protocol consists of

1. Team education and consensus on the use of sedatives in pediatric patients supported on mechanical ventilation,
2. Team identification of the patient's trajectory of illness and daily prescription of a sedation goal,
3. A Nurse-Implemented Goal-Directed Comfort Algorithm that guides moment-to-moment titration of opioids and benzodiazepines, and
4. Team feedback on sedation management performance.

Our data suggest that this protocol carries a remarkable potential to improve patient care. Our next step is a multicenter clinical trial of the pilot-tested pediatric sedation management protocol. Ultimately, confirming the benefit of this pediatric sedation management protocol will establish a PICU standard of care that will influence clinician education, care of all pediatric patients supported on mechanical ventilation, and future studies evaluating new or different combinations of sedative agents.

Specific Aims:

1. To conduct a multicenter clinical trial to test whether pediatric patients with acute respiratory failure managed per sedation protocol experience fewer days of mechanical ventilation than patients receiving usual care.
2. To describe the feasibility of the pediatric sedation management protocol in regards to financial cost.
3. To compare the post-discharge quality of life and emotional health in pediatric patients receiving sedation per protocol to those receiving it per usual care.

Primary Hypothesis: Pediatric patients with acute respiratory failure managed per sedation protocol will experience fewer days of mechanical ventilation than patients receiving usual care.

Primary endpoint: Duration of mechanical ventilation (equivalent to ventilator-free days).
Secondary endpoints: Time to recovery of acute respiratory failure, duration of weaning from mechanical ventilation, occurrence of adverse events, detection of life-threatening neurological events, total sedative exposure, occurrence of iatrogenic withdrawal symptoms, PICU and hospital length of stay (LOS), hospital costs, protocol implementation costs and cost-effectiveness, in-hospital mortality, and post-discharge quality of life and emotional health.

B. BACKGROUND AND SIGNIFICANCE

B.1 Sedation Management – A Serious Problem in the Pediatric ICU

Randolph and colleagues(8) completed a randomized controlled clinical trial comparing the use of ventilator management protocols to standard care in critically ill children. While the ventilator

management protocol had no effect on extubation failure rates or the duration of weaning from mechanical ventilation, increased sedative use in the first 24 hours of weaning predicted extubation failure (P=.004) and, among extubation successes, predicted more days of weaning (P=.001). Prolonging the duration of mechanical ventilation increases patient risk for ventilator associated complications; specifically, ventilator-associated pneumonia (VAP). (14-17) Observational studies have identified continuous sedation as an independent risk factor for VAP. (18)

To date, three national surveys describe wide variation in PICU sedation practices. (1-3) Most often, various combinations of opioids and benzodiazepines are used to sedate infants and children in the PICU. Opioids provide analgesia and benzodiazepines provide sedation, anxiolysis, and amnesia. The synergistic effect of combination therapy is often desirable in the PICU because the behavioral clues of pain and agitation in the pre/nonverbal intubated patient are often difficult to differentiate. Drug tolerance, defined as decreasing pharmacologic effect after repeated administration or increased requirements of a drug to achieve the same clinical effect, to opioids and benzodiazepines develops over time. (19-21) Iatrogenic withdrawal syndrome may occur when these agents are abruptly discontinued or weaned rapidly. (9-11, 22)

Opioids and benzodiazepines are administered by intermittent bolus dosing or by continuous infusion. Intermittent bolus dosing results in a cyclical pattern of over and under sedation and increases the nurse's workload in managing controlled substances. Although continuous infusion therapy provides a more consistent level of sedation, Kollef and colleagues (23) reported that continuous intravenous sedation was associated with prolongation of mechanical ventilation, increased intensive care and hospital lengths of stay, and higher reintubation rates when compared with intermittent sedation strategies or no sedation in adult critically ill patients. Arnold and others (9, 10) demonstrated that plasma concentrations of fentanyl required for satisfactory sedation steadily and rapidly escalate after 48 hours of continuous administration in neonates. Tolerance may develop more rapidly with a continuous infusion therapy. (10)

In a 2004 survey of pediatric critical care fellowship directors, 94% reported iatrogenic withdrawal syndrome as a problem in their units. (3) Iatrogenic withdrawal syndrome includes the physical signs and symptoms that manifest when the administration of an analgesic or sedative is abruptly discontinued in a patient who is physically tolerant. (21, 24, 25) Franck and colleagues (25, 26) describe the problem of iatrogenic opioid and benzodiazepine withdrawal in critically ill neonates and children and suggest a method of assessment. Classic symptoms of opioid withdrawal include signs of neurological excitability, gastrointestinal dysfunction, autonomic instability, and poor organization of sleep states. Benzodiazepine withdrawal symptoms are similar but also include agitation, visual hallucinations, facial grimacing, small amplitude choreic or choreoathetoid movements and seizures.

Based upon work by Arnold et al. (9, 10) and Katz et al. (27), a cumulative fentanyl dose >1.6 mg/kg and/or a duration of >5 days are considered risk factors for the development of iatrogenic withdrawal syndrome. Franck and colleagues (26) compared opioid withdrawal in infants receiving continuous morphine or fentanyl during extracorporeal membrane oxygenation (ECMO). Infants who received continuous morphine infusion required significantly less supplemental analgesia, had fewer withdrawal symptoms after discontinuation of therapy, and were discharged from hospital over one week sooner than infants who received continuous fentanyl infusion during ECMO. Compared to morphine, Tobias also noted that tolerance may develop more rapidly with fentanyl. (21) Fonsmark et al. (11) reported 35% prevalence of benzodiazepine withdrawal in 40 children receiving sedation during mechanical ventilation. A cumulative midazolam dose >60 mg/kg was significantly associated with withdrawal; duration of the infusion was not significant.

Iatrogenic withdrawal syndrome is currently prevented by a slow analgesic and/or benzodiazepine taper that may prolong PICU care. Treatment options include increasing or

reintroducing the opioid or benzodiazepine, conversion to long-acting oral agents, for example, methadone and lorazepam, (28) or introducing another sedative, hypnotic agent or an alpha-2 adrenergic agonist (clonidine). Continued PICU monitoring is recommended during opioid conversion as incomplete cross-tolerance contributes to inconsistent results.

Thus, while sedation helps keep patients safe and comfortable, sedation also depresses spontaneous ventilation and may prolong the duration of mechanical ventilation. (4, 5, 7, 8, 13) Over time, drug tolerance develops and may precipitate iatrogenic withdrawal syndrome when the patient no longer requires sedation. (3, 9-11)

B.2 Critically ill, Developmentally Immature Patient Populations Present Unique Challenges

Unique to the pediatric patient, cognitive immaturity prevents infants and young children from understanding the imperative nature of critical care instrumentation and immobility during life-sustaining invasive procedures. Preverbal patients are particularly disadvantaged. Developmentally they are unable to discuss their comfort level or talk to clinicians about their fears and concerns and often cannot express themselves non-verbally.

Most infants and children supported on mechanical ventilation are sedated to the point of no distress with as needed medication. (1) Therapeutic goals include analgesia, anxiolysis, facilitation of mechanical ventilation and amnesia. (1, 2) Pain is a common phenomenon for most critically ill patients. (29) Inadequate pain management may contribute to agitation. Similar to early nursing recommendations, (30) the most recent Society of Critical Care Medicine clinical practice guideline (2002) recommends that sedation be provided only after providing adequate analgesia and management of reversible physiological causes of agitation. (31) Although pain may cause anxiety in critically ill patients, patients may suffer from anxiety even after analgesia is addressed. Patients with acute respiratory failure are at high risk because ventilator management, for example, permissive hypercapnea and/or nonphysiologic modes of mechanical ventilation, may be inherently distressing to some patients. (32) Patients with acute respiratory failure also have little reserve to compensate for an increase in oxygen consumption associated with inadequate sedation management. Sedative administration reduces oxygen consumption an average of 15%. (33) Intuitively, amnesia of unpleasant events would seem desirable. However, in critically ill adults, increased sedation in general, and benzodiazepines in particular, are associated with long-term psychological distress, including post-traumatic stress disorder (PTSD). (34-37) Whether children, who process their illness and medical care quite differently than adults due to cognitive immaturity, benefit from amnesia is unknown.

Comfort practices are optimized by the use of valid and reliable assessment tools. In pediatrics, pain assessment tools vary per developmental age. Behavioral pain scales that do not require active patient participation are commonly used in pediatric patients supported on mechanical ventilation, for example, the FLACC (Facial expression, Leg movement, Activity, Cry, and Consolability) (38, 39) and Individualized Numeric Rating Scale (INRS). (40, 41) The INRS, an adaptation of a standard numeric rating scale (NRS), asks parents and nurses to identify an individual patient's typical pain behavior then stratify that behavior on a NRS scale of 0 (no pain) to 10 (worst possible pain). Curley developed the INRS to help PICU nurses observe, consistently document and communicate the unique pain behaviors of intubated, nonverbal, critically ill children after major surgical procedures. (40, 41) Several sedation scales, for example, the Sedation-Agitation Scale (SAS), (42) Motor Activity Assessment Scale (MAAS), (43) and the Richmond Agitation-Sedation Scale (RASS) (44, 45) have been developed for use in the adult ICU population. For critically ill pediatric patients, Curley and colleagues first modified the MAAS for PICU, (46) then completed psychometric testing of the State Behavioral State (SBS). (47)

Developmental limitations in communication and cognition may limit diagnostic evaluation of delirium in preverbal PICU patients. Delirium, a disturbance of consciousness characterized by

reduced awareness of the environment and the ability to focus, sustain and shift attention may present as severe agitation in the intensive care unit (ICU). (48) Delirium has been well described in adult ICU patients and has been associated with an increased hospital stay and higher morbidity and mortality rates. (49-51) Although pediatric patients are vulnerable to toxic, metabolic, or traumatic central nervous system insults, are at greater risk of delirium with fever regardless of the etiology, (52) and are typically sleep-deprived in the PICU, (53) delirium has been only anecdotally reported in PICU. (54-56) Prospective evaluation of at-risk pediatric patients may be warranted.

Ideally, sedation practices could be optimized if the pharmacokinetic and pharmacodynamic profiles of sedatives in critically ill pediatric patients were well described. Unfortunately, critically ill patients frequently exhibit unpredictable pharmacokinetic profiles. (57) Many critically ill patients have altered hepatic and/or renal function that impairs drug clearance. (58) Drug–drug interactions, altered protein binding, and circulatory instability are also common. In the ICU, sedatives typically exhibit multi-compartmental pharmacokinetics with a tendency for accumulation in the peripheral compartment and resulting prolongation of clinical effect.

The effect of prolonged exposure to opioids and benzodiazepines on infants and young children with a developing brain is also unclear. (59-62) The human central nervous system is not fully developed at birth and undergoes intense postnatal maturation. For example, the weight of the brain triples by 12 months of age. To approximately 2 years of age, neurons migrate to their final destinations and form uncountable synaptic connections to accommodate incoming axonal connections, setting the stage for a synchronized formation of meaningful neuronal circuitries. (63) There is some evidence, from studies in newborn rats, that opioid exposure causes long-term behavioral effects (64) and may retard growth and motor development. (65) In humans, MacGregor and colleagues assessed the outcome of 87 preterm infants (<34 weeks of gestation) who received short-term (2-5 days) morphine vs. no analgesia in the neonatal period to facilitate mechanical ventilation. While they found no significant differences in intelligence, motor function, or behavior at 5-6 years of age, the subjects receiving morphine had a trend towards improved outcomes. (66) Unfortunately, larger studies and studies of babies and older children receiving longer-term sedation are lacking.

B.3 Strategies for Intensive Care Sedation in Adults

Sedation practices vary widely between institutions, partly because of clinician bias (2) and partly because the sedation requirements vary greatly from patient to patient. (37, 67) In adult intensive care, the ultimate goal of sedation has evolved from an unresponsive state to a calm, easily aroused, readily evaluated, critically ill patient. (42, 68, 69) Successful sedation strategies reported in the adult ICU include daily prospective identification of an appropriate sedation endpoint and nurse-implemented protocols that include a daily wake-up test and/or titration of sedation. (5, 7)

B.3.1 Daily prospective identification of an appropriate sedation endpoint

Identifying a daily goal for sedation helps to guide the development of a treatment plan avoiding the administration of inappropriately high or suboptimally low pharmacologic agents. (5, 42, 69) Because deep sedation is more desirable than unmanaged agitation, clinicians often aggressively sedate patients early in their intensive care course but fail to titrate sedation when the patient's condition stabilizes or improves. Clinicians may initially overshoot the patient's initial sedation requirement and, unless the initial goals are reviewed and the agents titrated on a daily basis, patients may remain on inappropriately high dosages of sedatives for prolonged periods of time. (70)

B.3.2 Nurse-implemented protocols that include a daily wake-up test and/or titration of therapy

Two papers have revolutionized sedation practices in the adult ICU. First, Brook and colleagues (5) conducted a randomized, controlled clinical trial of 321 adult subjects comparing a practice

of protocol-directed sedation during mechanical ventilation implemented by nurses with traditional non-protocol-directed sedation administration in an adult medical ICU. The protocol required an initial assessment of analgesic and sedative needs. A Ramsay Sedation Scale (71) score of 3 was targeted (patient awake, responds to commands only). If frequent (more than every 2 hours) rebolus administration of opiates (fentanyl) or benzodiazepines (lorazepam) was required, continuous infusions of these drugs were started. Reassessment every 4 hours and downward titration of infusion rates were targeted until the infusion(s) was (were) stopped. Their findings were quite remarkable. The median duration of mechanical ventilation was significantly shorter by more than 2.5 days for patients managed with protocol-directed sedation (56 hrs; 95% CI 41-90 hrs) when compared to patients receiving non-protocol-directed sedation (117 hrs; 95% CI, 96-156 hrs). Lengths of ICU stay (5.7 ± 5.9 days vs. 7.5 ± 6.5 days; P=.013) and hospital stay (14.0 ± 17.3 days vs. 19.9 ± 24.2 days; P<.001) were also shorter among patients in the protocol-directed sedation group. Among patients receiving continuous intravenous sedation, those in the protocol-directed sedation group had a shorter duration of continuous intravenous sedation than those in the non-protocol-directed sedation group (3.5 ± 4.0 days vs. 5.6 ± 6.4 days; P = .003). Study limitations include lack of blinding, control of cointerventions and monitoring for protocol compliance and adverse events.

Second, Kress and colleagues (7) showed that daily interruption of all sedative infusions (wake-up test) reduced many of the complications of sedation infusions in an adult ICU setting. Kress et al. evaluated patients who received either midazolam and morphine or propofol and morphine by continuous infusion. Patients were randomized to either a daily scheduled interruption of the sedative and opiate infusions until patients were awake and could follow instructions (or until they became uncomfortable or agitated) after which the infusions were restarted at half their previous rates versus infusions managed by the primary ICU team without a mandatory daily interruption. In the interruption group, the duration of mechanical ventilation was reduced by 2.5 days, and ICU LOS was reduced by 3.5 days. Furthermore, Kress et al. reported a significant reduction in diagnostic studies to investigate unexplained alterations in mental status (27% control, 9% intervention). The patients in the sedative interruption group spent the vast majority of their ICU days awake and able to follow commands (average of 86% of ICU days) compared with the control group patients, who averaged only 9% of their ICU days awake and able to follow commands. The amount of midazolam and morphine administered was also significantly reduced in the group of patients who underwent daily sedative interruption. Although clinicians were blind to study outcome, blinding to group assignment was incomplete and the intervention (interruption of sedatives) occurred in approximately 30% of the control group. Furthermore, interventions known to impact the length of ventilation, for example, extubation readiness testing were not implemented; and the study was underpowered to assess patient safety.

The strategy of daily sedative interruption allows a focused downward titration of analgesic and sedative infusion rates over time, which minimizes the tendency for accumulation of sedative medications. By turning sedative infusions down or off, the drugs are redistributed from the tissue stores back into the circulation. The strategy also eliminates clinician tendency to accept the status quo at an inappropriately high (or low) sedative infusion rate. Anecdotally, rather than objectively, Kress et al. (72) reported less iatrogenic withdrawal in patients subjected to daily sedative interruption.

Responding to the criticism that more awake patients may be more traumatized by the ICU, (73) Kress et al. compared the long-term psychological impact of a daily wake-up test in adult patients managed with and without the intervention 6 months after hospital discharge. (72) They found that few patients recalled awakening from sedation even when it occurred on a daily basis, and signs and symptoms of post-traumatic stress disorder occurred less frequently in those undergoing daily interruptions. In adult ICU's, the Institute for Healthcare Improvement (IHI) Saving 100,000 Lives campaign recommends the use of a daily wake-up test to shorten

the length of mechanical ventilation as part of its VAP prevention care bundle. (http://www.ihi.org/IHI/)

Recently, Girard and colleagues (74) conducted a multicenter randomized trial testing a protocol that paired spontaneous awakening trials (daily interruption of sedatives) with spontaneous breathing trials in mechanically ventilated adult patients. The protocol resulted in more ventilator free days (3.1 additional days in the 28-day study, 95% CI 0·7-5.6), earlier discharge from both intensive-care units and hospitals, and better 1-year survival than patients in the control group, who received usual care that included patient-targeted sedation and a daily spontaneous breathing trial.

To better substantiate the need for this clinical trial, we conducted a 5 question, web-based survey of the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network; 109 physicians from 38/51 PALISI sites (75%) responded. We asked physicians about their sedation practices in ventilated children, their opinion about the strength of evidence (including both pediatric and relevant adult evidence), and their opinion on the practice's risk/benefit ratio. If more than one physician responded per center, we calculated the percent agreement within each center.

Sedation Practice Survey (August-September 2006) N=109			**% Using practice**	**% Agreement within Center**
1. Manage pediatric patients with an anticipated length of ventilation <2 days with intermittent sedative dosing as opposed to continuous sedative drips?			56%	25%
	Adequate Pediatric Evidence	**Favorable Risk-Benefit Ratio**		
2. Prescribe sedation where a nurse assesses the patient's level of sedation then titrates sedatives according to a protocol.	48%	84%	41%	31%
3. Perform daily wake-up tests in pediatric patients in a phase of illness when they are considered stable.	50%	71%	28%	19%
4. Wean narcotics over time in patients receiving narcotics for ≥ 5 days as opposed to abrupt discontinuation.	68%	94%	92%	44%
5. Assess daily, by protocol, for extubation readiness.	62%	85%	42%	28%

Survey results indicate that there is no uniform standard of care in how sedation is managed in pediatric patients supported on mechanical ventilation. In fact, there appears to be substantial variation in practice. Most believe that the risk-benefit ratio is favorable, but aside from weaning narcotics in a high-risk group, single elements of the sedation protocol are only practiced by 28-56% of the respondents. Only 9% say they practice all five elements. In addition, there is wide practice variation within each center.

B.4 Implementing Change in a Complex Environment

In the intensive care environment, Ibrahim and Kollef note that protocols can ensure that complex tasks are carried out in a timely manner. (75) Cabana et al. (76) conducted a systematic review of the literature on practices and factors impacting clinician adherence to practice guidelines. Their conceptual framework described a model sequence for implementing change: changing knowledge, then attitude, then behavior. Considering this framework, change requires a multimodal approach. Active educational programming and supportive educational material will impact clinician knowledge. Facilitating agreement, self-efficacy, outcome expectancy, motivation and feedback will impact clinician attitude. Reducing perceived and actual external and system barriers will impact behavior. Clemmer and Spuhler (77) note that in developing protocols, attention to changing the thinking and practice of front-line practitioners, establishing new relationships and devising new methods of delivering and improving care is

key. As intensive care practice has evolved so has the concept of team and collective responsibility for patient outcomes. (78)

B.5 Economic Impact of Changing Sedation Management

With rising healthcare costs, economic evaluations are increasingly important to thoroughly understand the societal impact of new therapies. Estimates of costs can inform decision makers (clinicians, hospital administrators, health care policy makers) and planning services that maximize health benefits. Cost evaluations are particularly important when a therapy is likely to be widely used and may affect intensity of care. The sedation of critically ill children is such a therapy. The costs associated with mechanical ventilation of US children have been estimated to be $1 billion per year in the US (79), and Osterman et al. recently called for economic evaluations specifically in studies of sedative agents. (80) In addition, implementing protocolized sedation can involve significant logistic challenges, including time, expertise, training, and oversight, all potentially costly. These costs may be offset by decreased resource use and better clinical outcomes leading to decreased downstream costs. An understanding of the enabling strategies required to promote the algorithm, which we will capture in these analyses, will be important in guiding its widespread implementation.

B.6 Relevant Clinical Outcomes in the Study of Sedation in the PICU

Relevant clinical outcomes in the study of sedative practices in the PICU include therapeutic success and a thorough evaluation of patient risk. Therapeutic success includes [1] analgesia; [2] anxiolysis; and [3] facilitation of mechanical ventilation while limiting the duration of mechanical ventilation (that matches the patient's lung disease); [4] faster recovery from acute respiratory failure; [5] limited duration of weaning from mechanical ventilation; [6] bolstered ability to remain successfully extubated; [7] an awake state that allows a more thorough evaluation of consciousness and earlier detection of life-threatening neurological events; [8] less total exposure to sedatives; [9] less iatrogenic withdrawal syndrome; [10] shortened PICU length of stay; and [11] lower costs. Evaluation of patient risk includes assessment of [1] adverse events; [2] mortality; and [3] post-discharge quality of life and emotional health.

B.7 Significance

In summary, efforts to provide a humane PICU experience and to facilitate mechanical ventilation can interfere with a rapid and complication-free recovery from acute respiratory failure. Rather than seeking an elusive ideal drug, the proposed study focuses on optimal clinical decision making. The proposed intervention models the most recent Society of Critical Care Medicine sedation clinical practice guideline (31) and addresses the only manipulable factor influencing extubation failure rates in the PICU. (8) Kollef and colleagues (13) noted that sedation practices should be standardized in any investigation employing the duration of mechanical ventilation as an outcome variable. This study provides a team approach to help improve sedation management of critically ill infants and children supported on mechanical ventilation for acute respiratory failure and will provide economic and follow-up outcome data that will enhance both patient-centered and socially-relevant aspects of health policy. The study has the potential to significantly impact the care of the vast majority of critically ill infants and children with acute respiratory failure by developing a generalizable strategic approach that optimizes patient comfort and tolerance of invasive support.

C. PRELIMINARY STUDIES

C.1 Development of a Nurse-Implemented Goal-Directed Comfort Algorithm

A multidisciplinary task force designed and implemented eight progressive drafts of the Nurse-Implemented Goal-Directed Comfort Algorithm over 2 years. (81) This algorithm is designed to provide clinicians with an analytical framework for the evaluation and management of pain and agitation in critically ill infants and children supported on mechanical ventilation. The overall goal of the algorithm is to ensure patient comfort and use of the lowest effective dose of a limited number of analgesics and sedatives for the shortest period of time in patients supported on mechanical ventilation.

Changes in practice also included pain and sedation scoring at a minimum of every four hours. Page one, Box one of the algorithm calls for an assessment of the patient's pain. After pain and reversible causes of agitation have been excluded and environmental comfort measures have been provided, the priority is targeted to achieve a desired state behavior as quickly as possible. Continuous opioid and benzodiazepine infusions are only prescribed when the predicted length of intubation is greater than 2 days. Once on continuous infusions, pain relief continues to be a priority and the team identifies the patient's trajectory of illness and prescribes a sedation goal that matches the patient's trajectory of illness every day during multidisciplinary rounds. PICU nurses then titrate the sedatives using the Nurse-Implemented Goal-Directed Comfort Algorithm and a standardized order sheet.

Compared with the work of Brook et al. (5) and Kress et al. (7), unique features of this algorithm include matching the therapeutic goal to the patient's trajectory of illness, wake-up test and mandated titrations every 8 hours only during the plateau phase, a rapid opioid wean followed by a slow benzodiazepine wean, and use of a longer acting agent (methadone) only in symptomatic patients. (82) During quality monitoring of the final version of this algorithm, wake-up tests durations were 90 minutes (median; IQR: 60-150 minutes). Kress and colleagues (37) anecdotally reported an average wake-up test of 50 minutes in their adult medical ICU patients. The Nurse-Implemented Goal-Directed Comfort Algorithm is currently the standard of care in the Medical-Surgical PICU at Children's Hospital Boston.

C.2. Sedation Management in Pediatric Patients Supported on Mechanical Ventilation

This three-year project [5R21HD045020], led by Dr. Curley, pilot-tested the pediatric sedation management protocol in patients supported on mechanical ventilation for acute respiratory failure in two different children's hospitals: Children's National Medical Center (CNMC) and Children's Hospital Wisconsin (CHWisc). Our hypothesis and outcomes are similar to that presented in Section A, but we used a pre-post test design and did not include patient follow-up. The two units were randomized to either "early" or "late" intervention. That is, both PICUs provided baseline data on their usual sedation practices for 9 months then one PICU was randomized to start the intervention phase "early" while the second PICU continued to collect baseline data. After 9 months, the second PICU started the intervention phase "late" while protocol sustainability was evaluated in the first PICU.

During the start-up phase, all nurse and physician coinvestigators attended a start-up meeting to discuss Children's Hospital Boston's experience with the Nurse-Implemented Goal-Directed Comfort Algorithm. System nuances were discussed and the study coinvestigators reached consensus on all study protocols. After the start-up meeting, training on the pain and sedation assessment tools, WAT, and extubation readiness test (ERT) was initiated. The Principal Investigator visited both PICUs to support staff education and to establish interrater reliability on the assessment tools. Baseline data collection began and after 3 months study enrollment was lower than predicted. Predicted enrollment was based on what each site coinvestigator thought they could enroll after their review of the study inclusion/exclusion criteria; their predictions were not data-based. Both PICUs expected to provide data on at least 20 patients per month but, on

average, only 10 patients per month were enrolled. The Steering Committee voted to extend the study period from 2 to 3 years and the study timeline was adjusted.

In November 2004, CNMC was randomized to the early intervention PICU. Team education occurred in the month prior to implementation. This training was mandatory for all clinicians (physicians, nurses, clinical pharmacists) involved in the sedation management of intubated mechanically ventilated patients. Training materials were developed by the research team and included discipline-specific lectures, a self-learning packet, bedside booklets, and standardized order sheets. The coordinating center produced a training video on the Nurse-Implemented Goal-Directed Comfort Algorithm and videotaped a wake-up test on a 3-year-old child. The Principal Investigator re-visited CNMC during the first week of implementation to assist with protocol implementation. Weekly “walk-round” reports were generated by the Data Coordinating Center (DCC). These “walk-round” reports described protocol compliance and coinvestigator follow-up and provided the team with feedback on their sedation management performance during the intervention phase.

In August 2005, CHWisc began enrolling intervention patients and CNMC entered into the sustainability phase. CHWisc training was similar to CNMC but the PICU used Staff Nurse Champions to disseminate the accountability for training and implementation. CHWisc also used a computerized order entry system that made changes to the order sheet easier to accomplish. Both PICUs were able to complete initial multidisciplinary training in one month then continued to provide monthly training to physicians-in-training rotating through the PICUs and orientation to newly hired nurses and respiratory therapists. Our Data and Safety Monitoring Board (DSMB) reviewed study progress and adverse event data. Patient enrollment ended April 30, 2006 and data entry and analysis were complete by December 2006.

Over 27 months, 2095 pediatric patients supported on mechanical ventilation were screened and 245 patients (12%) met study criteria and were enrolled; 128 patients from CNMC (site 1; 45 baseline, 46 intervention period, 37 sustainability) and 117 patients from CHWisc (site 2; 80 in baseline and 37 in intervention periods). Common reasons for patient exclusion included congenital heart disease (24%); no pulmonary disease (30%); and ventilation for immediate post-operative care (22%). Enrolled patients were 2.4 years old (median; interquartile range; IQR 0.5-11.3 years), 54% male, with predominately normal cognitive development and functional health as measured by the pediatric cerebral performance category (PCPC) and pediatric overall performance category (POPC). (83) Common reasons for mechanical ventilation included pneumonia (38%), bronchiolitis (17%), and thoracic trauma (10%). Median Pediatric Risk of Mortality III (PRISM III) scores were 9 (IQR: 5-17) with an associated risk of mortality of 5% (median; IQR 2-22%). (84) Race and ethnicity breakdown were as follows: 44% Black, 38% White, 15% Hispanic, and <1% Asian, American Indian or more than one race. Consistent with their patient demography, Site 1 enrolled significantly more black patients (P>.001).

Duration of mechanical ventilation, the primary outcome, was available for 193 patients (excluding the 37 sustainability patients). Per our pilot-study analysis plan, excluded were 15 patients (7%) who died before the outcome was observed by Day 28. Table C. 2.1 gives the comparison for each site. Median duration of mechanical ventilation decreased in both sites. After adjusting for age group, PRISM III score and POPC at enrollment, the adjusted hazard ratio (HR) for being off mechanical ventilation was 1.79 (95% CI 1.12-2.87; P=0.02) for site 1 and 0.89 (95% CI 0.57-1.38; P=0.59) for site 2. Using an analysis adjusting for age group, PRISM III score, POPC at enrollment, and site and assuming a common HR across the two sites, the estimated adjusted HR was 1.24 (95% CI 0.91-1.67; P=0.17), which corresponds to a 19% (–10% to 40%) reduction in median duration if the duration is exponentially distributed. These Phase 2 data show a strong, significant positive effect in Site 1 and a non-significant negative effect in Site 2. Combined, these data support the current Phase 3 application.

Table C.2.1 Primary Outcome - Duration of Mechanical Ventilation

	Site 1 CNMC (N=84)		Site 2 CHWisc (N=109)	
	Baseline	**Intervention**	**Baseline**	**Intervention**
Number of subjects	42	42	72	37
Hours Median (Q1,Q3)	141 (95, 256)	107 (62, 159)	177 (101, 246)	162 (91, 323)
Unadj. HR* (95% CI)	1.72 (1.10-2.68)		0.86 (0.56-1.31)	
Adjusted† HR* (95% CI)	1.79 (1.12-2.87)		0.89 (0.57-1.38)	
Adjusted† HR* Adjusted for Site (95% CI)	1.24 (0.91-1.67)			

*Intervention versus control; †Adjusted for age group, PRISM III and POPC>1 at enrollment.

The analyses of secondary outcomes are summarized in Table C. 2.2. In general, trends in the intervention phase included a shorter period of weaning from mechanical ventilation and decreased PICU and hospital lengths of stay. Patients in the intervention group also tended to have less narcotic exposure and were at less risk for withdrawal. Benzodiazepine exposure decreased in Site 1 but increased in Site 2. Pain scores were similar in the two groups at both sites. Patients were more sedated during the intervention phase in Site 2.

Table C.2.2 Secondary Outcomes

	Site 1 CNMC			Site 2 CHWisc		
Outcome	**Baseline**	**Intervention**	**P Value***	**Baseline**	**Intervention**	**P value***
Time to recovery of ARF (hours)†	N=37 96 (57,139)	N=37 72 (38,152)	0.60	N=64 112 (66,201)	N=33 105 (69,188)	0.61
Duration of weaning from mechanical ventilation (hours)†	N=37 26 (4, 53)	N=37 15 (4, 31)	0.16	N=64 28 (6, 57)	N=33 25 (2, 60)	0.17
Day 28 mortality	7% (3/45)	9% (4/46)	0.71	10% (8/80)	5% (2/37)	0.41
Length of PICU stay (days)	N=40 10 (6,16)	N=42 7 (4,10)	0.31	N=71 10 (6,15)	N=34 8 (5,16)	0.56
Length of hospital stay (days)	N=39 17 (11, 24)	N=41 14 (9, 21)	0.98	N=70 19 (12, 39)	N=34 15 (9, 24)	0.06
Total Morphine Equivalents (mg/Kg)	N=39 13 (4, 49)	N=42 7 (3, 22)	0.20	N=71 16 (1, 59)	N=34 8 (3,15)	0.66
Total Midazolam Equivalents (mg/Kg)	N=39 13 (6, 46)	N=42 8 (4, 21)	0.21	N=71 5 (1, 9)	N=34 10 (4, 19)	0.001
Average daily pain score (1-10 scale)	N=45 0.1 (0, .4)	N=46 0 (0, .2)	0.17	N=80 0 (0, .2)	N=37 0 (0, .2)	0.89
Average daily sedation score (MMAAS: –3 to +3)	N=45 –.4 (–.8, 0)	N=46 0 (–.8, .3)	0.24	N=80 0 (–.6, .7)	N=37 –.6 (–1, 0)	0.04
Duration of weaning from sedation (days)	N=20 11 (8, 15)	N=12 11 (6, 17)	0.91	N=28 12 (8, 20)	N=9 14 (9, 18)	0.80
Risk for iatrogenic withdrawal (>5days)	59% (23/39)	44% (18/41)	0.18	57% (40/70)	53% (18/34)	0.69
Nurses peak NRS (1-10 scale) ratings of withdrawal	N= 17 2 (1-4)	N=9 3 (1-4)	0.87	N=20 3 (2-5)	N=8 3 (2-5)	0.94
Peak WAT-1 scores (1-12 scale)	N=20 2 (0-3)	N=13 3 (1-4)	0.10	N=28 5 (2-7)	N=10 6.5 (6-9)	0.08
"Withdrawal" WAT-1 score >3‡	30% (6/20)	62% (8/13)	0.07	71% (20/28)	90% (9/10)	0.24

Frequency of Neurological Tests	49% (22/45)	35% (16/46)	0.17	40% (32/80)	38% (14/37)	0.82
Unplanned extubation rate§	2.6 (8/311)	4.3 (12/280)	0.27	0.6 (4/713)	1.2 (4/336)	0.31

* Log rank tests for duration of mechanical ventilation, time to recovery, duration of weaning, length of PICU stay; Fisher's exact tests for in-hospital mortality, ever at risk for withdrawal, ever had neurological test; exact binomial test for unplanned extubation rate. † The adjusted hazard ratio (adjusted for site, age group, PRISM III and POPC>1) was 1.02 (95%CI 0.74-1.40; P=0.91) for time to recovery, and 1.52 (95%CI 1.10-2.10; P=0.01) for duration of weaning from mechanical ventilation. ‡ WAT-1 ≥ 3 in patients who were at risk of withdrawal (sedatives >5 days) and assessed for withdrawal. § Unplanned extubation rate per 100 ventilation days (number of events/number of ventilation days)

From a safety perspective, unplanned extubation rates were different between the two sites and increased in both sites during the intervention phase. Of the 16 unplanned extubations that occurred during the intervention phase, 10 occurred during the titration of sedatives (6 plateau phase of illness - all patients reintubated; 4 weaning to extubation phase - no patient reintubated). No unplanned extubations occurred during a wake-up test. The combined rate in the two sites during the intervention phase was 2.6 (16/616). Published adult and pediatric critical care unplanned extubation rates range from 0.25 to 3.0/100 ventilator days (85-89).

In terms of protocol compliance, the phase of illness was identified in 996/1024 (97%) treatment days. Sedation scores (MMAAS) progressively decreased over the patient's trajectory of illness; specifically, the median MMAAS was –.82 (IQR –1.33, 0) in the acute phase, –.25 (IQR: –1, 0) in the plateau phase, and 0 (IQR: 0, 0) in the weaning to extubation phase ($p < .001$). Only 2 patients were not awake at 8am (MMAAS –2 or –3) during a plateau phase day; both patients were withdrawn from life support. Wake-up tests were performed in 13 patients and lasted a median of 290 minutes (IQR 75-2160 minutes). One patient did not awaken during a wake-up test allowing early detection of an intracranial bleed. Prolonged wake-up tests occurred in four patients with impaired renal function. Prior to extubation, 84% of all patients were tested for extubation readiness. Seventy-one percent of patients were weaned from sedation according to the algorithm. Protocol deviations related to weaning included both acceleration (27%) and slowing (36%) of the process.

To estimate costs associated with the protocol, we multiplied resources consumed by subjects by cost weights derived from 1999 hospital discharge data from six states (FL, MA, NJ, NY, VA, and WA represent 22% of the US population), procedure costs from the Medicare Relative Value Payment Amount, and physician costs as an additional 17% of hospital costs. To estimate implementation costs, we multiplied personnel time reported by sites for protocol training and ongoing monitoring by mean national hourly wages from the US Bureau of Labor statistics and the American Association of Medical Colleges. We added mean implementation costs per subject to the hospital costs for intervention patients. All costs were adjusted to 2005 US$ using the Consumer Price Index. Because this study was not randomized, we also constructed a general linear model to assess the degree to which differences in log-transformed costs were associated with the intervention, controlling for PRISM score, age, gender, and study site.

Protocol implementation costs averaged $20,760 per site and $500 per intervention subject. Intervention subjects consumed fewer hospital resources; baseline hospital costs were $70,640 (mean; $55,390 median) and intervention hospital costs were $61,660 (mean; $35,940 median), a difference of $8,980 ($19,450), P=0.01. When adjusting for patient characteristics and severity of illness, costs were not significantly lower among intervention subjects (P=0.095), suggesting that at least some of the cost difference may be attributed to differences in patient characteristics between baseline and intervention phases. However, given the relatively small sample size of this pilot study, the lack of statistical significance may be related to a lack of power rather than an absence of effect. In addition, intervention patients incurred fewer CNS-

related diagnostic tests, with average costs of $195 per patient (vs. $322 in the baseline phase, P=0.18).

At the end of the study, the Principal Investigator debriefed each clinical site. Based on our findings and clinician feedback, we revised the intervention to enhance patient safety and strengthen protocol oversight:

- Actively monitor for all sedation-related adverse events during daily investigator walk rounds;
- Link the wake-up test to the patient's SBS; specifically, perform a wake-up test if the patient's SBS is –3 or perform a modified wake-up test (only reduce the sedative infusions by 50%) if the patient's SBS is –2;
- Rename the "plateau phase" to the "titration phase" to remind staff not to entrain the status quo;
- Simplify the algorithm by matching the frequency of drug titration to every 8 hours in the titration and weaning to extubation phases;
- Perform the ERT when the patient meets ERT criteria;
- Slow narcotic weaning in the weaning to extubation phase from 20% every 12 hours to 10% every 8 hours;
- Trend WAT-1 scores and expect some withdrawal symptoms in high-risk patients but intervene if the patient is intolerant of withdrawal symptoms;
- Critically review all unplanned extubations and episodes of SBS ≥ 1; specifically, evaluate sedation level, trajectory of illness, time from last sedative titration, patient activity, nurse-patient ratio, nurse presence at the bedside, potential for delirium;
- Emphasize the sedation goal of (1) awake yet comfortable patients and (2) minimal adverse events.

D. INVESTIGATORS

The investigation team for this study includes the Principal Investigator and coinvestigators who bring expertise in the pediatric sedation management protocol, iatrogenic withdrawal syndrome, clinical trial design in critical care settings, and the long-term follow-up of complex patients. Collaborating coinvestigators include coinvestigator teams at each of approximately 26 clinical sites.

D.1 Principal Investigator & Core Investigators

Martha A.Q. Curley, RN, PhD, the Principal Investigator, is an expert in the nursing care of critically ill infants and children and their families. She has extensive experience in managing change in complex organizations and in the conduct of clinical research studies. Dr. Curley was the principal investigator for a multisite randomized controlled clinical trial of prone positioning in pediatric patients with acute lung injury (ALI). (90)

Brenda Dodson, PharmD, Core coinvestigator, is an Academic and Pediatric Navigator at Cerner Corporation. Dr. Dodson is an expert in the pharmaceutical care of critically ill infants and children. Dr. Dodson will provide expertise on the selection and use of sedative drugs, staff training, and protocol implementation.

Rainer Gedeit, MD, Core coinvestigator, Medical Director of Respiratory Care Services, Associate Medical Director PICU, Chief of Medicine at Children's Hospital of Wisconsin. Dr. Gedeit is a Pediatric Intensivist and expert in pediatric ALI and mechanical ventilation. Dr. Gedeit will assume a major role in assisting clinical teams implement the protocol within their practice settings.

Deborah J. Soetenga MS, RN, CCRN, Core coinvestigator, is the Advance Practice Nurse for the PICU and Cardiovascular Surgery department at Children's Hospital of Wisconsin. Ms. Soetenga will assume a major role in assisting clinical teams implement the protocol within their practice settings.

Linda Franck, RN, PhD, Core coinvestigator, is the Professor and Chair of Children's Nursing Research, jointly appointed by the University College Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust. Dr. Franck will provide expertise on opioid and benzodiazepine withdrawal assessment.
Michael A. Matthay, MD, Core coinvestigator, is a Professor of Medicine and Anesthesia at the University of California at San Francisco and a Senior Associate at the Cardiovascular Research Institute. He is Director of the Critical Care Medicine Training in the Department of Medicine and Associate Director of the Intensive Care Unit. Dr. Matthay will provide advisement on key decisions during the clinical trial to the Principal Investigator.

D.2 Data Coordination Center (DCC)

The Statistics and Data Coordinating Center of the Department of Cardiology at Children's Hospital Boston will perform the DCC role for this trial. DCC staff for this study includes the Principal Investigator/Senior Biostatistician of the DCC, a Biostatistician, a Project Manager, a Survey Specialist, an Applications Developer, a Data Manager, and a Data Coordinator.

David Wypij, PhD, Principal Investigator/Senior Biostatistician of the DCC, is a Senior Biostatistician at Children's Hospital, Boston, Associate Professor of Pediatrics at Harvard Medical School, and Senior Lecturer on Biostatistics at Harvard School of Public Health. Dr. Wypij has considerable experience in the leadership of DCC efforts for single- and multi-center studies, with special expertise in PICU management, surgical follow-up studies, and pediatric cardiology. Dr. Wypij will direct all DCC efforts for this new study.

The DCC will:

- Provide overall study coordination, including development of study forms and manual of operations, training of study personnel, participation in Steering and Operational committees, and coordination of Data and Safety Monitoring Board meetings.
- Support study monitoring and create data reports for the Data and Safety Monitoring Board.
- Provide data management and data quality services, including database development, database checks and updates, quality control and quality assurance, site monitoring visits, maintenance of patient confidentiality, and firewalls.
- Perform all data analyses for the main study, support publication and abstract preparation, assist with the rapid dissemination of findings, and create final data sets for archiving.
- Coordinate with the Clinical Research, Investigation, and Systems Modeling of Acute Illness Center at the University of Pittsburgh for the cost and post-discharge studies.

D.3 Follow-up & Economic Evaluation

The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, University of Pittsburgh will conduct post-discharge telephone interviews and will perform analyses of the long-term outcomes and cost-effectiveness of the protocol. CRISMA staff include trained, Spanish-speaking interviewers who can complete translation and back translation of interview instruments (to and from Spanish) as needed.
R. Scott Watson, MD, MPH, Core coinvestigator, is an Assistant Professor of Critical Care and Pediatrics at the University of Pittsburgh. He is a core faculty member of the CRISMA Center. Dr. Watson will provide expertise on the economic analysis and the follow-up components of the trial.
Derek C. Angus, MD, MPH, Core coinvestigator, is a Professor of Critical Care Medicine and Health Policy and Management at the University of Pittsburgh. He is the Director of the CRISMA Center at the University of Pittsburgh School of Medicine. Dr. Angus will mentor the team in the economic and follow-up components of the trial.

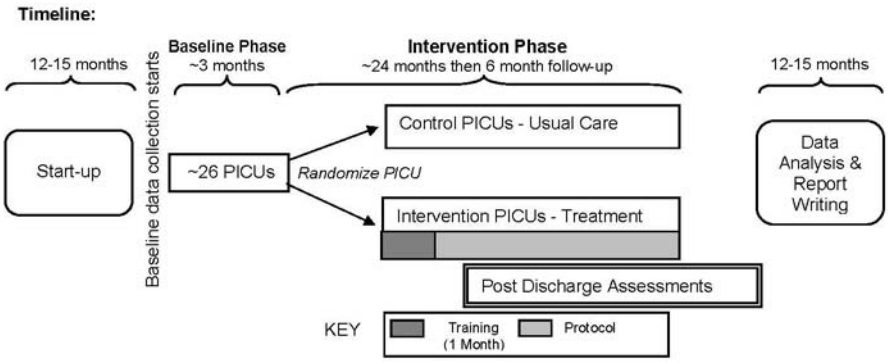
D.4 Collaborating Centers

Approximately 26 PICUs will collaborate in this research. Each participating center includes a physician-advanced practice nurse-pharmacist coinvestigator team. All PICUs were required to (1) submit a completed mock screening form that provided an actual account of unit volume over a month's time, and (2) to complete a nine-page organizational assessment that described their unit's structure, work processes, change processes and a description of their unit's comfort practices (brief summary included in the Appendix III). The PICUs were selected because they showed evidence that the study was formally reviewed by their nursing and physician leadership groups, agreed to the study design, and were expected to enroll a minimum of 3 patients per month. Each PICU uses standardized physician order sheets and nurses titrate routine PICU therapies within parameters prescribed during multidisciplinary rounds.

E. RESEARCH DESIGN AND METHODS

E.1 Study Overview

This is a multicenter cluster-randomized clinical trial that tests the effect of a pediatric sedation management protocol on the duration of mechanical ventilation in pediatric patients supported on mechanical ventilation for acute respiratory failure. The intervention is an organizational change directed at all PICU clinicians. The unit of randomization is the PICU, the unit of inference is the patient, and we will control for center effects. Patients in both groups will be followed from endotracheal intubation to the end of their scheduled sedation therapy, or until hospital discharge, or Day 28 (whichever occurs first). On Day 28 daily data collection will end but patients will be followed for outcomes. We will select a stratified random sample of subjects and their parents/legal guardians to whom we will administer a telephone-based follow-up interview approximately 6 months after PICU discharge to assess the patient's long-term quality of life, psychologic sequelae, and post-discharge health-related resource use.



All PICUs will provide baseline data for approximately three months, then approximately half of the sites will be randomized to implement the intervention as a research protocol while the remainder will continue to provide their usual care.

The PICUs will be classified into three groups (small, medium, and large) based on their completed mock-screening tools, organizational assessment forms and on their baseline phase enrollments.

This approach provides verifiable historical and recalibrated data on the number of patients who meet study enrollment criteria each month, PICU bed capacity, average PICU daily census, and the number of medical patients supported on mechanical ventilation in each PICU per month. The PICUs will be block randomized by group (small, medium, and large) and batch (first or second batch). Block randomization is necessary to assure a balanced allocation of similar PICUs between the control and intervention groups. Random assignment will be performed by DCC staff during the baseline data collection period after all start-up work has been completed.

Prior to baseline data collection, all centers will implement the same validated pain, sedation and withdrawal assessment instruments. Prior to randomization all sites will provide approximately 3 months of baseline data so that site comparability at trial entry can be

evaluated. After randomization, a start-up meeting with all coinvestigators from the intervention sites will be conducted. The purpose of this start-up meeting will be to review the R21 pilot experience with the pediatric sedation management protocol and to initiate protocol training. System nuances may impact site-specific protocol implementation and training and will require group discussion and team problem-solving.

After the start-up meeting, PICUs randomized to the intervention group will undergo one month of training and then begin to implement the pediatric sedation management protocol on all patients with acute respiratory failure as a research protocol. *RESTORE* training will be multifaceted and include all clinicians (physicians, nurses, clinical pharmacists) involved in the sedation management of intubated mechanically ventilated patients. In addition to the core physician-nurse-pharmacist team, each unit will identify additional multidisciplinary "Champions" to serve as unit-based resources on the *RESTORE* protocol within each unit. This Champion team will allow staff access to *RESTORE* protocol experts 24/7 and will also accommodate the monthly training schedules of new physicians-in-training and nurse orientees as per unit norm.

During the intervention phase, one of the site coinvestigators will alternate responsibility and round separately on each study patient each day to monitor for patient safety, adverse events, and *RESTORE* protocol compliance. During walk rounds, the site investigators will also offer staff support and retraining as necessary and complete the daily walk-rounds report. This level of vigilance is necessary to monitor patient safety and to identify aspects of the protocol that are challenging to clinicians so that support can be given. Also, an accurate reporting of protocol deviations requires an evaluation of the context of clinician decision-making. The walk-rounds reports will be summarized weekly so that team feedback on sedation management performance can be provided. All *RESTORE* sedation orders will be derived from a standardized *RESTORE* physician order template. The *RESTORE* physician order template will serve three purposes: reinforcement of training, decrease delays in implementing a change in a patient's analgesia and sedation and enhance protocol compliance.

E.1.1 Rationale for evaluating the pediatric sedation management protocol in a cluster randomized clinical trial

We considered randomization by patient, team, and PICU. We rejected patient randomization because the intervention requires a practice change in how clinical teams work together. Patient randomization could lead to group contamination over time. We rejected team randomization because multiple teams rotate in a PICU over the course of a day. We chose cluster randomization by PICU (91-94) to control for secular changes and limit contamination between groups. We have recruited approximately 26 PICUs to obtain high statistical power; all have agreed to the design where approximately half of the PICUs are randomized to the *RESTORE* intervention as a research protocol and the remaining PICUs continue usual care. The design will allow multiple comparisons within each PICU and between all PICUs. In addition, a multicenter clinical trial will allow potential bias to be distributed across diverse practice settings, allow the comprehensive assessment of patient risk, allow the determination of the level of protocol compliance necessary to assure desired patient outcomes, and increases the generalizability of study results.

E.1.2 Rationale for using duration of mechanical ventilation as the primary outcome variable

Sedation influences the duration of mechanical ventilation in patients with acute respiratory failure and interventions that both maintain patient safety and comfort are desirable in the critical care environment. Based on our pilot study, we believe this protocol will result in a 20% reduction in the duration of mechanical ventilation in this patient group. If supported, this outcome coupled with secondary outcome data will provide compelling evidence to change practice during protocol dissemination.

E.1.3 Rationale for secondary outcome variables

- Time to recovery of acute respiratory failure (from endotracheal intubation to first meeting criteria to be tested for extubation readiness): Matching the patient's sedation goal to their trajectory of illness should result in more awake and spontaneously breathing patients during the titration phase who may then be tested earlier for extubation readiness.
- Duration of weaning from mechanical ventilation (from first meeting criteria to be tested for extubation readiness to first successful extubation – defined as extubation for more than 24 hours): More awake patients may wean faster from mechanical ventilation and remain extubated.
- Occurrence of adverse events (specifically, inadequate pain management, inadequate sedation management, clinically significant iatrogenic withdrawal symptoms, unplanned extubation, airway irritation from movement of the endotracheal tube within the airway, extubation failure/reintubation within 24 hours of extubation, dislodgement of vascular access or drainage tubes, VAP, catheter-associated blood stream infection (CA-BSI), and stage 2+ pressure ulcers). The frequency of adverse events is a critical measure of treatment safety. More awake patients may experience more adverse events and may suffer more airway irritation from movement of an endotracheal tube within the airway. The occurrence of VAP and stage 2+ pressure ulcers have been directly attributed to level of sedation. CA-BSI is associated with duration of catheter placement and the number of interruptions into the closed system.
- Detection of life-threatening neurological events: Failure to awaken during a wake-up test may allow more rapid identification of an evolving neurological catastrophe. More awake patients may impact the necessary frequency of neurological testing (brain computerized tomography, brain magnetic resonance imaging, lumbar puncture) to evaluate state behavior.
- Total sedative exposure (total dose and length of exposure): *RESTORE* may decrease patient opioid and/or benzodiazepine exposure. This study is unique because all sedative use throughout the patient's hospital stay will be monitored.
- Occurrence of iatrogenic withdrawal symptoms: Less drug exposure may decrease the incidence of iatrogenic withdrawal syndrome but accelerated weaning may increase withdrawal symptoms.
- PICU and hospital LOS: Shortening the duration of mechanical ventilation should decrease LOS.
- Hospital costs: Reduced duration of mechanical ventilation may be associated with an important reduction in hospital costs that will enhance the value and acceptance of the sedation protocol.
- Protocol implementation costs: The advisability, feasibility, and generalizability of the sedation protocol will be influenced by the personnel time and effort.
- Cost effectiveness: Effective protocol implementation will require an investment of personnel time. However, reduced duration of mechanical ventilation could decrease downstream costs with improved (or unchanged) quality of life, making protocolized sedation a 'valuable' strategy with a favorable cost-effectiveness ratio. Incorporating estimates of costs and effects into a formal cost-effectiveness analysis will provide additional, important information on which to base protocol adoption into practice.
- In-hospital mortality: Critical measure of treatment safety.
- Post-discharge quality of life and emotional health: Sedation and analgesia provided to critically ill patients have effects that extend beyond hospital discharge and may not be predicted by in-hospital events. Multiple studies in animal models (95-97) and newborns (98-101) have found long-term behavioral and neurodevelopmental effects of pain and sedation. Studies of older children are few (102, 103) but effects undoubtedly vary with age and development. In adults, Kress et al. (72) found that a daily wake-up test had a beneficial long-term psychological impact 6 months after hospital discharge. Whether

changing the level of sedation among children will have similar long-term effects is unknown. Young children have limited cognitive and communication skills and may derive more benefit than adults from amnesia provided by higher levels of sedation. On the other hand, if the intervention decreases the duration of mechanical ventilation and PICU LOS, the decreased exposure to the PICU environment may outweigh any potential benefits derived from increased amnesia.

E.2 Eligibility and Recruitment

E.2.1 Subject eligibility

Patients in each PICU will be screened on a daily basis by the site coinvestigator or designee to determine whether they meet eligibility criteria. Subject eligibility criteria focus on pediatric patients with acute respiratory failure defined by the following inclusion and exclusion criteria.

E.2.1.a Inclusion Criteria

Consecutive intubated pediatric patients (≥ 2 weeks of age and ≥ 42 weeks post menstrual age and <18 years of age) supported on mechanical ventilation for acute lung disease. Lung disease includes both airways and parenchymal disease.

E.2.1.b Exclusion Criteria

Criteria focus on excluding patients in which the length of mechanical ventilation is unlikely to be altered by sedation management. Children will be excluded if they are/have any of the following at the start of assisted breathing:

- Cyanotic heart disease with unrepaired or palliated right to left intracardiac shunt
- History of single ventricle at any stage of repair
- Congenital diaphragmatic hernia or congenital/acquired diaphragm paralysis
- Primary pulmonary hypertension
- Critical airway (e.g., post laryngotracheal reconstruction) or anatomical obstruction of the lower airway (e.g., mediastinal mass)
- Ventilator dependent (including noninvasive) on PICU admission (chronic assisted ventilation)
- Neuromuscular respiratory failure
- Spinal cord injury above the lumbar region
- Pain managed by patient controlled analgesia (PCA) or epidural catheter
- Patient transferred from an outside ICU where sedatives had already been administered for more than 24 hours
- Family/medical team have decided not to provide full support (patient treatment considered futile)
- Enrolled in any other critical care interventional clinical trial concurrently or within the last 30 days
- Known allergy to any of the study medications.
- Pregnancy

Each patient will contribute one set of data. Specifically, in patients experiencing multiple unrelated PICU admissions, only the first PICU admission data will be evaluated.

E.2.2 Inclusion for post-discharge quality of life and emotional health

Stratified random sample of half of subjects enrolled in the trial whose parents consent to post-discharge follow-up. To ensure that the sample is representative of all subjects in the trial, the sample will be stratified by study site and age (<2 years, 2-4 years, 5-7 years, 8-12 years, and 13-18 years). Age groups are based on developmental stage and assessment tools to be used in each group.

E.2.3 Adequacy of the Available Population

In preparation for this study, each participating center was required to screen their PICU for one month using the pilot study screening forms. A natural grouping of PICUs who care for a similar volume of intubated patients with acute respiratory failure emerged: small, medium and large. Conservatively, we assumed enrollment at 18 sites, with a minimum of 3 subjects enrolled from each of the 6 small PICUs per month, 5 subjects from each of the 6 medium PICUs per month, and 9 subjects from each of the 6 large PICUs per month. Thus, at minimum, we anticipated that 18 sites would provide data on at least 102 patients per month. Based on this information, we calculated our minimum enrollment to be a total of 306 subjects in the baseline period (approximately 3 months) and 2448 study patients over approximately 2 years, which would meet our accrual needs. In our pilot study, 6% of parents refused or were unable to provide consent. The participating centers screened approximately 190 patients over the one month mock screening period (Fall 2005), so even with a 6-46% refusal rate, we expected to be able to enroll an average of 102 patients per month.

In 2009, the study began with 22 sites randomized in a first batch. Study enrollment was reviewed in June 2010. Enrollment rates from these 22 sites have been slightly lower than expected above. To increase enrollment rates, we will add additional sites in a second batch in 2010, following the same procedures as for the first batch. The target sample size for the intervention phase remains at 2448 patients, but now with up to 452 baseline and wash-in patients given the additional sites. Wash-in patients are those subjects who are enrolled during the training phase after a site has been randomized to the intervention group, but before the site is implementing the intervention. Wash-in patients will not be included in treatment group comparisons.

We will monitor study enrollment using the Daily Screening Logs each week. Based upon enrollment data, the Steering Committee could also elect to extend the intervention phase of the study to achieve adequate power. To avoid over-enrollment by site, each PICU will cap their monthly enrollment at three times their group's average monthly enrollment.

E.3 Study Treatments

During baseline data collection, patient sedation will be managed at the discretion of the care team and no recommendations will be made. Sites randomized to control will continue their usual care; specifically, unrestricted usual care. Sites randomized to intervention will manage patients with acute respiratory failure supported on mechanical ventilation per the *RESTORE* protocol. Patients in both groups will be followed from endotracheal intubation to the end of their scheduled sedation therapy, or until hospital discharge, or Day 28 (whichever occurs first). If the intubated/ventilated subject is not receiving sedation then they will be followed until successfully extubated or Day 28 (whichever occurs first).

In addition, we will assess psychologic sequelae in patients for post-discharge adverse events with a follow-up telephone interview and self-administration of standardized questionnaires at 6 months post-PICU discharge.

E.3.1 Care Provided during the Baseline and Intervention Phases

E.3.1.a Pain and Sedation Scoring every Four Hours

Pain and sedation levels will be scored separately at least every four hours using the same validated pediatric instruments. The pain assessment scale depends upon the age and verbal capacity of the patient: infant to 7 years: FLACC;(38) 3+ years of age: Wong-Baker Faces;(104) 5+ years of age, NRS; 6+ years of age and nonverbal: INRS. (40, 41) All pain scales range from 0-10. The State Behavioral Scale (SBS) will be used to assess sedation-agitation levels. (47) Clinicians will use their clinical judgment to identify pain and/or agitation in patients requiring neuromuscular blockade. For example, "assume pain present" (APP) and/or "assume agitation present" (AAP) when the patient experiences $\geq$ 20% increase in heart rate/blood pressure when stimulated.

E.3.1.b Assessment of Withdrawal Symptoms

Patients weaning from >5 days of opioids will be monitored for the occurrence of withdrawal symptoms using the same validated pediatric instrument, the WAT-1. (105) Withdrawal assessment will end 72 hours after the patient receives an opioid dose. During this interval the WAT-1 will be completed at least every 12 hours while the patient is in the PICU and at least every 24 hours while in the hospital.

E.3.2 Treatment with the Pediatric Sedation Management Protocol (*RESTORE*)

The pediatric sedation management protocol (*RESTORE*) consists of

1. Team education and consensus on the use of sedatives in pediatric patients supported on mechanical ventilation,
2. Team identification of the patient's trajectory of illness and daily prescription of a sedation goal,
3. A Nurse-Implemented Goal-Directed Comfort Algorithm that guides moment-to-moment titration of opioids and benzodiazepines,
4. Team feedback on sedation management performance.

The *RESTORE* protocol makes recommendations of which sedatives to use and when to use them in pediatric patients supported on mechanical ventilation.

During daily multidisciplinary rounds, the Nurse-Implemented Goal-Directed Comfort Algorithm directs clinicians to identify the patient's trajectory of illness and prescribe a daily sedation goal. The bedside nurse then uses the algorithm with matching standardized order sheet to titrate the sedatives to the prescribed SBS level. One of the site coinvestigators rounds separately on study patients and completes the walk-round report describing patient safety, adverse events, and protocol compliance. This weekly report forms the basis for the team feedback on sedation management performance.

The pediatric sedation management protocol manages pain first and reminds the clinician to exclude reversible causes of agitation prior to administering benzodiazepines. Patients remain on intermittent dosing of opioids and benzodiazepines unless the predicted length of intubation is greater than 2 days. To facilitate patient comfort and immediate control, doses may be repeated up to three times at ten minute intervals until the desired level of analgesia and/or sedation is reached. If patients are already receiving opioids and/or benzodiazepines prior to PICU admission then starting doses are adjusted. Once the patient is on continuous infusions, the patient's trajectory of illness and associated SBS level is identified each morning during multidisciplinary rounds (acute phase, titration phase, and ventilator weaning to extubation phase).

In the acute phase (defined as a phase in which the patient is considered unstable, interventions are escalating, the patient may require neuromuscular blockade to facilitate mechanical ventilation, and/or the patient is physiologically intolerant of PICU stress) the goal is to maintain the status quo and the desired SBS is –1 or less (–1: responsive to gentle touch or voice; –2: responsive to noxious stimuli; –3: unresponsive to stimulation) and no decreases in sedation are recommended.

In the titration phase (defined as a phase in which the patient is considered stable, intensive care interventions are not escalating, chemical paralysis is off, and the patient is or should be physiologically tolerant of PICU stress) the desired SBS is –1 or 0 (–1: responsive to gentle touch or voice; 0: awake and able to calm).The daily "wake-up"/arousal assessment test is performed if the patient is unresponsive (SBS–3); a "modified wake-up"/arousal assessment is performed if the patient is responsive only to noxious stimuli (SBS –2). The arousal assessment is initiated when the nurse can cluster care so that he/she can be vigilant of the patient. Analgesics and sedatives are discontinued followed by gentle stimulation every 5-10 minutes. When awakening patients, patients are safely brought to the brink of consciousness and assessed from a developmental perspective. This equates to a SBS of –1 (opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with touch or when name is spoken;

drifts off after stimulation; follows simple commands, for example, “squeeze my hand”). If the patient already scores a –1 on their SBS then an arousal assessment is not necessary. The arousal assessment is aborted if excessive agitation results. Although the attempt at waking and communicating with the patient may be declared a failure on a given day, previous failures are not predictive of subsequent failures. Accordingly, the arousal assessment is repeated each day after which sedatives are restarted at half of their previous dose (unless the arousal assessment is unnecessary or aborted in which case the sedative dose is not cut in half). With a modified arousal assessment, sedatives are reduced to half their previous dose; they are not turned off. Readjustments from this restarting point are made as required. Sedatives are then titrated every 8 hours to maintain the prescribed level of sedation. The arousal assessment is modified for the patient assessed to be in pain; for example, benzodiazepine changes are made but the morphine infusion is reduced by 50% at the start of the assessment then retuned to its full dose after the assessment.

In the ventilator weaning to extubation phase (defined as a phase in which the patient passes an extubation readiness test) sedatives are weaned depending on the patient’s length of therapy. Sedatives are discontinued if the patient received <5 days of sedation. If the patient received ≥ 5 days of sedation, opioids are tapered over 72 hours. The benzodiazepine infusion is then converted to intermittent lorazepam intravenous bolus injections followed by enteral dosing then weaned over 5-10 days.

Patients who meet extubation readiness test (ERT) criteria are tested each morning and the results are discussed during multidisciplinary rounds. If the patient fails their ERT they are returned to their pre-test ventilator settings and re-tested the next morning. If the patient fails the ERT because of excessive sedation, the care team may elect to wean the patient’s sedation (per protocol) and retest the patient at 4 PM the same day. If the patient does not meet extubation criteria at 4 PM they are returned to their pre-test ventilator settings and re-tested the following morning. If the patient passes the ERT (meets criteria for unassisted breathing from a pulmonary perspective) the bedside team may attempt extubation or choose to keep the patient intubated for nonpulmonary reasons. The decision of the clinical team is recorded in the electronic case report form (eCRF).

E.3.3 Post-discharge quality of life and emotional health

Detailed neurodevelopmental testing of subjects is beyond the scope of this study; however telephone and mail-based assessments of functional status, quality of life, and emotional well being is feasible.

Consent for follow-up assessment 6 months post-PICU discharge will be sought from the parents or legal guardians. Patients will be asked to provide assent when they are cognitively capable; specifically, patients over 8 years of age, with a Pediatric Cerebral Performance Category of 1-3 (normal to moderate disability), 72 hours after their last sedative dose. Adolescents, turning 18 after study enrollment, will be asked to provide consent. If the subjects do not assent, they will not be included in the follow-up. For Spanish-speaking subjects, we will conduct interviews in Spanish. We will utilize existing Spanish translations of all instruments when available. We will translate other instruments into Spanish and verify the accuracy of the translation with independent back-translation to English.

After receiving a reminder letter and copies of the standardized assessment instruments by mail, consenting families will be called 6 months (± 1 month) after PICU discharge. We will interview the subjects’ parents to assess subject’s functional status and post-discharge health care resource use. In addition, we will ask parents and subjects age 8 and older to complete standardized quality of life assessment questionnaires, either on the internet or via mail. Subjects age 8 and older will also be asked to complete a standardized PTSD assessment questionnaire (similarly via internet or mail). The interview will take 7 to 20 minutes to complete,

depending on the age of the subject, and the questionnaires will take 5 to 14 minutes to complete.

E.4 Study Outcomes

E.4.1 Duration of mechanical ventilation - Primary outcome

The primary outcome for this study is the duration of mechanical ventilation. For patients orally or nasally intubated, the duration of mechanical ventilation is the number of days and hours that the patient is intubated. Removal of the ETT will be calculated from the first time the tube is continuously absent for at least 24 hours. (106) Definition of assisted breathing is any pressure support ≥5 cmH_2O even if applied non-invasively (for example, BiPAP). Definition of unassisted breathing includes extubation with/without supplemental oxygen, tracheotomy mask breathing, and mask/nasal CPAP <5 cmH_2O without pressure support (PS) or intermittent mandatory ventilation (IMV) assistance. Should reintubation be required within 24 hours, suspected cause and date/time will be recorded in the eCRF.

The duration of mechanical ventilation in patients who die during the first 28 days of the study will be assigned the worst possible outcome (28 days of mechanical ventilation) unless the nonsurvivor remained extubated for >24 hours prior to death. This mortality-adjusted duration of mechanical ventilation is a continuous variable that is effectively equivalent to using ventilator-free days. (107, 108) Ventilator-free days will also be calculated. It is highly unlikely that any acutely ill intubated child would be transferred to another care facility. If transfer does occur, this outcome will be censored on Day 28.

E.4.2 Time to recovery of acute respiratory failure – Secondary outcome

This will be computed as the time from endotracheal intubation to the time that the patient first meets criteria to be tested for extubation readiness. The time to recovery of acute respiratory failure in patients who die during the first 28 days of the study will be excluded unless the nonsurvivor met criteria for extubation readiness testing prior to death. It is highly unlikely that any child with an oxygenation index >6 would be transferred to another care facility. If transfer does occur, this secondary outcome will be censored on Day 28.

E.4.3 Duration of weaning from mechanical ventilation – Secondary outcome

This will be computed from the time the patient first meets criteria to be tested for extubation readiness to successful endotracheal extubation (extubated for >24 hours). For patients who have tracheotomies, time of weaning from mechanical ventilation will be defined as the time they first meet ERT criteria to successful removal of assisted breathing. The duration of weaning from mechanical ventilation in patients who die during the first 28 days of the study will be excluded unless the nonsurvivor is extubated for more than 24 hours prior to death. If the patient is transferred to another facility prior to weaning from mechanical ventilation, this secondary outcome will be censored on Day 28.

E.4.4 Occurrence of adverse events – Secondary outcome

Adverse events that will be specifically monitored include inadequate pain management, inadequate sedation management, clinically significant iatrogenic withdrawal symptoms, unplanned extubation, airway irritation from movement of the endotracheal tube within the airway, extubation failure/reintubation within 24 hours of extubation, dislodgement of vascular access or drainage tubes, VAP, catheter-associated blood stream infection (CA-BSI), and stage 2+ pressure ulcers. The VAP rate, defined as the number of VAP per 1,000 ventilator days, will be defined as pneumonia occurring ≥ 48 hours after initiation of mechanical ventilation. (109) The CA-BSI rate, defined as the number of CA-BSI per 1,000 central line-days, will be defined as bacteremia/fungemia in a patient with an intravascular catheter in use during the 48-hour period before the development of the bloodstream infection. The National Nosocomial Infections Surveillance System (NNIS) definitions will be used to define VAP and CA-BSI. All cases of VAP and CA-BSI will be adjudicated by a process outlined by Cook et al. (110) and approved by the Steering Committee. Pressure ulcers will be staged according to National Pressure Ulcer

Advisory Panel recommendations (111) and attribution assigned using the Braden Q scale. (112) Definition and treatment of serious adverse events are described in Section F.6. VAP and CA-BSI will be assessed up to 24 hours of PICU discharge. Report of a new critical airway will be assessed through hospital discharge or Day 90 (whichever occurs first).

E.4.5 Detection of life-threatening neurological events – Secondary outcome
Failure to awaken during an arousal assessment may allow more rapid identification of an evolving neurological disaster (intracranial bleed, cerebral edema) that might otherwise have gone undetected. More awake patients may impact the frequency of neurological testing to evaluate state behavior. We will compare the proportion of patients who require neurological testing before and after protocol implementation.

E.4.6 Total sedative exposure – Secondary outcome
All opiates will be converted to morphine sulfate equivalents using the following conversions to equal 1 mg of intravenous morphine sulfate: 15 micrograms intravenous fentanyl citrate, 0.15 mg intravenous hydromorphone hydrochloride, 0.3 mg intravenous or enteral methadone hydrochloride, and 20 mg enteral codeine phosphate. All benzodiazepines will be converted to midazolam equivalents using the following conversions to equal 1 mg intravenous midazolam: 2 mg intravenous diazepam, 0.33 mg intravenous or enteral lorazepam. We will record the cumulative (mg/kg), mean daily (mg/kg/day), and peak daily (mg/kg) doses in morphine and midazolam equivalents. (24) The cumulative dose will be calculated by summing the daily dose of each agent (scheduled and PRN) over the entire PICU admission and dividing by the patient's dosing weight. The mean dose will be calculated by dividing the cumulative dose by the number of days the specific drug was administered in the PICU. The peak dose will be highest dose of each drug administered on any one day to the patient while in the PICU. The total number of days the patient received comfort medications will also be recorded. The use of all adjunctive agents will also be recorded.

E.4.7 Occurrence of opioid and benzodiazepine withdrawal symptoms – Secondary outcome
WAT-1 scores ≥ 3 are indicative of clinically significant iatrogenic withdrawal symptoms.(105) Presence and intensity of withdrawal symptoms are assessed on a 12-hourly basis and consist of three indicators obtained from the nursing documentation in the previous 12 hours (loose/watery stools, vomiting, temperature elevation), three indicators assessed during a 2 minute observation of the patient at rest (sweating, yawning, state behavior), four indicators assessed during a progressive arousal stimulus (startle, tremor, muscle tone, uncoordinated movements), and one indicator (time to return to calm state) assessed during an observation period following the stimulus.

E.4.8 PICU and hospital length of stay – Secondary outcome
PICU LOS is defined as the time from PICU admission to the date and time the physician orders are written for PICU discharge. Hospital LOS is defined as the time from hospital admission to hospital discharge. The PICU LOS in patients who die during the first 28 days of the study will be excluded unless the nonsurvivor is discharged from the PICU for more than 24 hours prior to death. Hospital LOS in patients who die during the first 28 days of the study will be excluded.

E.4.9 Hospital costs – Secondary outcome
Hospital costs will be estimated by collecting information on resource use in the eCRF and multiplying resources consumed by US cost weights derived from external cost databases. We will estimate hospital costs from the PICU LOS with and without mechanical ventilation, ward LOS, and physician costs. We will multiply lengths of stay by daily cost weights for the different types of hospital days: mechanically ventilated PICU and not mechanically ventilated PICU and ward. We will obtain the daily cost weight through analysis of public-use hospital discharge data from six states representing 22% of the US population, which we have used previously (113-115) and from the High Density Intensive Care database, which contains detailed clinical, cost,

charge, and resource use data on the hospital course for all 6,000 ICU admissions per year to the University of Pittsburgh Medical Center. We will generate the cost weights from total hospital costs and lengths of stay (estimated using Centers for Medicare and Medicaid Services [CMS] cost-to-charge ratios) for hospitalized children (excluding children admitted for post-operative care or receiving chronic mechanical ventilation via a tracheostomy) using the latest year of data available at the time of analysis and adjusting to Y2012 US$ as appropriate. We will estimate the physician costs during hospitalization as an additional 17% of hospital costs. (116, 117) In addition, we will estimate costs of sedative medications and CNS-related diagnostic tests for subjects based on hospital acquisition costs for each sedative and procedure reimbursement rates from the CMS. Finally, we will collect data on post-discharge health care resource use (rehospitalizations, ED visits, physician visits) and will estimate costs from the Medicare fee schedule and outpatient prospective payment system. We are aware that these estimates (and those for implementation costs described in the following section) may not reflect true costs in practice, and will therefore expose their uncertainty through extensive sensitivity analyses.

E.4.10 Implementation costs – Secondary outcome

We will estimate the mean costs per site for training and ongoing monitoring, based on clinician participation in training efforts, effort spent by *RESTORE* Champions, and a portion of the effort spent by the site coinvestigator providing feedback and quality monitoring. Some efforts are only expended once, and will be amortized over the length of data collection. Clinician hours will be multiplied by average national wage rates from the Bureau of Labor Statistics. (118) Summed implementation costs will then be divided across the mean annual number of eligible patients per site to generate a mean implementation cost per patient.

E.4.11 Cost-effectiveness – Secondary outcome

We will conduct this analysis following the principles and recommendations of the US Public Health Service Panel on Cost and Effectiveness in Health and Medicine (PCEHM) (119) and the American Thoracic Society (ATS) position statement on Understanding Costs and Cost-effectiveness in the Critically Ill. (120) We will use methods developed as part of our prior and ongoing cost-effectiveness assessments of other interventions and monitoring tools for sepsis, shock, and respiratory failure. (121, 122) The PCEHM recommends generation of a Reference Case, (123) which is a cost-effectiveness ratio calculated under a set of standard assumptions and methods to facilitate the comparison of cost-effectiveness ratios across studies. However, assumptions related to the development of a Reference Case may be problematic in studies of critical illness. (120) In pediatric critical illness in particular, the generation of a Reference Case is hindered by the lack of established methods to assign utilities to infants and young children. (122) Therefore, the cost-effectiveness analysis will focus on the ATS-recommended Base Case, which is predicated on a shorter time horizon and requires fewer assumptions. (120)

E.4.12 In-hospital mortality – Secondary outcome

Deaths from all causes will be monitored through hospital discharge or Day 90 (whichever occurs first). To ensure complete data, the primary and secondary causes of death (as specified on the death certificate) will be recorded and summarized.

E.4.13 Post-discharge quality of life and emotional health – Secondary outcome

Functional status will be assessed using the PCPC and POPC (83) (2 items, <2 min. to complete), which will also be obtained from parents in-hospital to record subjects' baseline functional status. These scales were developed as modifications of the Glasgow Outcome Score (124) and classify children to one of six broad categories. They have high validity and reliability, (83, 125, 126) and are recommended by the American Academy of Pediatrics, American Heart Association, and the European Resuscitation Council for the reporting of outcomes associated with pediatric resuscitation. (127)

To assess quality of life in children under the age of 2 years, we will use the Infant Toddler Quality of Life Questionnaire (ITQOL) (103 items, 14 minutes to complete, http://www.healthact.com/surveys_itqol.html). The ITQOL is the only quality of life instrument validated for use in infants. (128) It measures 14 unique physical and psychosocial concepts, including general health; change in health; physical functioning; bodily discomfort; limitations in school, work, and activities; behavior, mental health, self-esteem, impact of illness on parents, limitations in family activities, and family cohesion. Scores can be analyzed separately or combined to derive an overall physical or psychosocial score.

In children 2 years and older, we will use the Pediatric Quality of Life Inventory, Version 4.0 (129) (PedsQL) (23 items, <5 min. to complete, http://www.pedsql.org). The PedsQL evaluates health-related quality of life in 4 areas: physical, emotional, social, and school-based functioning. It has been found to be valid, reliable, and have high internal consistency. Particular advantages of this measure are its inclusion of items that assess non-physical functioning and well being, the availability of validated and straightforward child self-report forms, and its brief administration time. (130-133) Parent-report will be solicited in all ages, and children aged 8 years and older will be asked to self-report. If the parent of an older child has difficulty completing the PedsQL due to a child's significant developmental impairment (eg, children with a PCPC or POPC >3), the ITQOL will be used.

In children age 8 and older with a PCPC $\leq$ 3, we will also administer the Child Posttraumatic Stress Disorder (PTSD) Symptom Scale (134) (24 items, <5 min. to complete), which assesses all PTSD symptoms in the three clusters of DSM-IV. (135) It is the only pediatric PTSD scale including items corresponding to all 17 DSM-IV symptoms and 7 questions related to functional impairment. This validated instrument has high internal consistency and test-retest reliability. (136)

E.5 Measurement of Study Variables

E.5.1 Methods of Data Collection

Site coinvestigators will be trained in data collection methods by the DCC Project and Data Managers prior to enrolling patients. (see E.9.2)

E.5.2 Data Collection Schedule

The data collected during baseline and intervention phases (both control and intervention groups) will allow the description of sedation practices during the baseline phase and in the usual care arm and the comparison of treatment group differences.

E.5.2.1 Table – Data Collection

Measurement	Screening	Start of scheduled sedation therapy	Daily	End of study period
Demographic Data	X	X		
Patient History and Problem List	X	X		
Admission PRISM III Score		X		
PCPC Score		X		X
POPC Score		X		X
Intubation and Ventilation Status		X	X	X
Use of Chemical Paralysis		X	X	
Pain and SBS Scores		X	X	
All Sedative Agents		X	X	X
Neurological Status		X	X	
WAT-1			X	
Adverse Events		X	X	X
Patient Summary				X

Intervention Group				
Protocol Compliance		X	X	X

While Dr. Curley and her research staff will have access to summary reports (as appropriate) within the study database, they cannot view or change any study data, as they are assigned low-level access, only allowing the ability to print out certain reports. In addition, Dr. Curley will not be involved in the development or distribution of DSMB reports.

E.5.3 Screening

The medical records of all intubated PICU patients will be screened daily for the presence of inclusion criteria and for the absence of exclusion criteria. This Health Insurance Portability and Accountability Act (HIPAA)-compliant database will also provide the registry of potentially eligible patients to determine whether a representative number of females, minorities and pulmonary disease cohorts have been enrolled in the study. Patients who meet study criteria but who do not consent to participate or miss the enrollment window will be noted.

E.5.4 Baseline Assessment

A baseline assessment will be completed on all patients. The form includes demographic data, medical history information, primary cause for acute respiratory failure, admission PCPC and POPC (83) and admission PRISM III. (84) PRISM III score will be used to describe pediatric patient acuity (84) and is derived from 17 physiologic variables subdivided into 26 ranges computed using the most abnormal values during the first 12 hours of PICU admission. Higher scores are associated with more severe physiologic instability and higher mortality. Parents of subjects consenting for post-discharge follow-up will also complete a socioeconomic status and basic baseline health questionnaire.

E.5.5 Daily Assessment

All patient's ventilation status, chemical paralysis use, pain and sedation scores, WAT-1 scores, and all comfort medication (drug, dose, route, frequency) will be collected everyday. All adverse events in both groups will be monitored. The site coinvestigators will also monitor patient safety, adverse events, and protocol compliance during their daily walk rounds.

E.5.6 End of Study Form

The End of Study Form will be completed upon hospital discharge. The End of Study Form lists dates crucial to the study, specifies the functional status of the subject, and identifies the location of PICU and hospital discharge.

E.6 Study Safety

Patients will be monitored daily for the occurrence of adverse events defined as any untoward or unfavorable occurrence. A description of all events will be recorded on eCRFs. The relationship of sedation to the event will be classified as not related, possible, probable, or definitely related by the bedside team. The severity of an adverse event will be classified as mild, moderate, or severe by the bedside team. Site coinvestigators will report unanticipated, related or possibly related problems to their internal IRBs, the DCC and Dr. Curley within 24 hours. Dr Curley and local coinvestigators will immediately follow up on these problems and communicate with the DSMB and external IRBs per NIH guidelines. Site coinvestigators will report all serious adverse events (SAEs) to the DCC within 24 hours. All serious, unexpected adverse events that are possibly, probably or definitely related to the intervention will also be reported to Dr. Curley within 24 hours. Dr. Curley and local coinvestigators will immediately follow up on these SAEs and communicate with the DSMB and external IRBs per NIH guidelines. In addition, we will assess psychological sequelae in patients for post-PICU discharge adverse events with a follow-up assessment at 6 months post-PICU discharge.

E.6.1 Support for Data and Safety Monitoring Board Meetings

Before each DSMB meeting, the study biostatisticians will prepare a written report. The report will include the following topics (plus any other topics requested by DSMB):

- Update overall status of the study, recruitment, and accrual

- Summary of baseline characteristics
- Information on data completeness, data quality, protocol compliance, and other quality-control measures
- Statistical summary of adverse events
- Statistical summary of primary and key secondary outcome variables.

These topics will be grouped into an open section containing information to which the investigators are not blinded (items up to adverse events) and a closed section containing information to which the investigators are blinded (outcomes and events broken down by treatment). The full report will be distributed to the DSMB and the open section of the report to the investigators one to two weeks in advance of the meeting, and then reviewed during the meeting. The investigators will participate in the first part of DSMB meetings to present the open section of the report and answer questions from the DSMB, and then be excused for the closed session. After each meeting, the DSMB will make a statement regarding the quality of the study and safety of participants and write a brief recommendation either to continue the study without changes or to modify the study in specific ways. This recommendation will be submitted by the investigators to the IRBs at or prior to the next annual IRB review of the study. We plan to perform three formal interim analyses after study outcomes have been obtained on approximately 400, 1200, and 1800 subjects, for the DSMB to assess whether or not to stop the study early for efficacy or futility. There will also be a review of study endpoints and adverse events by the Data and Safety Monitoring Board at these times, or as requested by the Data and Safety Monitoring Board.

E.7 Statistical Considerations

The primary aim of the study is to compare the clinical outcomes in children supported on mechanical ventilation managed per sedation protocol vs. no protocol. The study design is a multi-center cluster-randomized clinical trial. All PICUs will provide baseline data for approximately three months, and then approximately half of the sites will be randomized to the intervention, while the remaining sites will continue to provide their usual care. A first batch of 22 PICUs began study enrollment in 2009. To increase enrollment rates, a second batch of PICUs will begin study enrollment in 2010. Outcome variables are designed to be as objective as possible since it is not possible to blind the assessor to treatment assignment. The primary outcome for this study is the duration of mechanical ventilation. The DCC biostatisticians will be responsible for all statistical analyses for the main study; the analysis of economic and post-discharge outcomes will be performed by the CRISMA team at the University of Pittsburgh.

E.7.1 Cluster Randomization Design

Cluster randomized trials are being increasingly used in biomedical intervention studies, particularly for quality improvement trials, health care interventions, and educational strategies in which the intervention occurs at a practice or group level. In this case, individual subjects are not independent; subjects from the same cluster may be correlated with one another. There has been extensive recent interest in the design and analysis of cluster randomized trials, (92-94, 137-141) including literature reviews, (142, 143) many applications, (144, 145) three books, (146-148) theme issues of journals, (149, 150) and an extension of the CONSORT statement for cluster randomized trials. (91) This study design requires an assessment of within-cluster vs. between-cluster variability in order to determine the required sample sizes to achieve sufficient power, as cluster randomized designs generally need increased sample sizes to accommodate within-cluster correlations. It also requires a statistical analysis plan that adjusts for within-cluster correlations. A cluster randomized design is particularly helpful to consider when interventions are at the cluster level, and randomizing individuals to the interventions being compared could lead to treatment contamination. This design may also be able to control for secular trends provided the trends were similar in the treatment groups being compared, and

which could confound a pre-post comparison design (e.g., baseline (usual care) crossing over to a later intervention in all sites).

E.7.2 Randomization Schema and Process

The PICUs will be classified into three groups based on their completed mock-screening tools and organizational assessment forms and on their baseline phase enrollments. This approach provides verifiable historical and recalibrated data on the number of patients who would potentially meet study enrollment criteria each month in each PICU and the number of medical patients supported on mechanical ventilation in each PICU per month. The PICUs will be block randomized by group (small, medium, and large) and batch (first or second batch) to assure a balanced allocation between the control and intervention arms. Among each block, approximately half will be randomized to receive the intervention, and the reminder to continue usual care, using a computerized random assignment program. Random assignment will be performed by DCC staff near the end of the baseline data collection period after all start-up work has been completed, separately for each batch.

E.7.3 Preparation of the Analysis Data Set

Datasets for analyses consist only of data for which all queries have been resolved. In addition to the data management steps described above to reduce error in data acquisition and entry, a biostatistical cleaning will focus on inconsistencies, missing data, and outliers in variables related to the derivation of key outcomes, and on documenting heterogeneity across sites. These activities will be ongoing throughout the study and will involve both the data management team and the biostatistics team.

Preplanned construction of new variables will be conducted in accordance with the study hypotheses and analysis plans. Variable transformation may be required for interpretive and statistical purposes. With respect to the primary outcome, duration of mechanical ventilation, subjects who are still intubated after 28 days, and subjects who die prior to day 28 and who had not remained extubated for >24 hours prior to death, will be viewed as censored at 28 days, the worst outcome. This mortality-adjusted duration of mechanical ventilation is a continuous variable that is effectively equivalent to using ventilator-free days (108) as the primary outcome. Despite extensive efforts in the follow-up of study subjects and in the process of data management, missing data may occur. For analysis of the primary outcome, missing values due to loss of follow-up will be imputed by conservatively assuming the patient is on ventilator on any day when the “ventilator status” is unknown. Sensitivity analyses treating these values as censored at the last follow-up day will also be performed.

E.7.4 Statistical Analysis Plans

The primary outcome for this study is the duration of mechanical ventilation. Secondary outcomes include time to recovery of acute respiratory failure, duration of weaning from mechanical ventilation, occurrence of adverse events, detection of life-threatening neurological events, total sedative exposure, occurrence of iatrogenic withdrawal symptoms, PICU and hospital length of stay, hospital costs, protocol implementation costs and cost-effectiveness, in-hospital mortality, and post-discharge quality of life and emotional health.

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. Transformations will be undertaken as needed. Comparisons of demographic and baseline variables by treatment group will control for PICU as a cluster variable through the use of generalized estimating equations or mixed effects models.

Specific Aim 1: Our primary analysis will compare the duration of mechanical ventilation in 1224 control vs. 1224 intervention subjects using Kaplan-Meier survival curves and proportional hazards regression. We will also collect data on up to 452 baseline and wash-in subjects. For our primary analysis of duration of mechanical ventilation, we will consider PICU as a cluster

variable in survival analyses (using Lin and Wei's sandwich variance estimator). (151) For primary analyses, the duration of mechanical ventilation in patients who die during the 28-day study period will be censored at 28 days, provided the subject had not remained extubated for >24 hours prior to death. This mortality-adjusted duration of mechanical ventilation is a continuous variable that is effectively equivalent to using ventilator-free days (108) as the primary outcome. This method for handling mortality is a conservative approach in that deaths (among subjects who had not remained extubated for >24 hours prior to death) are equated with the longest duration of ventilation values.

We anticipate that the mortality rate in the first 28 days will be low and similar between the control and intervention groups. Our pilot sedation management study had an overall 28-day mortality rate of 7%, which was similar in the baseline and intervention phases. If that holds in the proposed study, we will also perform a secondary analysis excluding these deaths from the analysis, effectively to compare the duration of mechanical ventilation among survivors. If the mortality rate is higher than anticipated and/or is unbalanced between control and intervention patients, we will also conduct a competing risks analysis, treating extubation and death as two competing events. (152, 153) In addition, we will compare control vs. intervention patients in the binary outcome of whether or not there was a successful extubation during the first 28 days, treating the nonsurvivors as failures if they are not extubated for >24 hours prior to death. This analysis will be performed using logistic regression and generalized estimating equations or mixed effects models to control for PICU as a cluster variable. Other analyses of the primary outcome variable will control for variables such as severity of illness (admission Pediatric Risk of Mortality III (PRISM III) score and POPC>1) and age (<2 years, 2-6 years, >6 years). An alternative analysis approach for the primary outcome variable will be based on a permutation test of the median duration of mortality-adjusted duration of mechanical ventilation across the sites.

For analyses of secondary outcomes, we will use proportional hazards regression for time to event outcomes, linear regression for continuous outcomes, and logistic regression for binary outcomes to control for variables that are likely to be associated with outcomes, including severity of illness (admission PRISM III score and POPC>1), age (<2 years, 2-6 years, >6 years), disease process (variation in the duration of acute and/or titration phase), and use of chemical paralysis. Through all analyses, we will use generalized estimating equations or mixed effects models (including Lin and Wei's sandwich variance estimator (151) for time to event outcomes) to control for PICU as a cluster variable. For non-normal continuous outcomes, we will consider data transformations or nonparametric methods, as appropriate.

We do not expect secular or time trends in treatment (due to seasonal variation or learning effects) for primary or secondary outcomes, but we will carefully examine for them. We will examine all data for time trends, and, if necessary, we will adjust for time in regression models. We will also assess whether varying levels of protocol compliance results in varying levels of intervention effects using correlation and regression methods. Throughout, residual analyses will be performed to assess the appropriateness of modeling assumptions and check for outlying or overly influential observations.

Interim Analysis Plans: An independent Data and Safety Monitoring Board will monitor this clinical trial for adverse events, adherence to study protocol, and potential early stopping. The trial may be stopped if any of the following occur:

- The intervention is associated with an increased dependency on mechanical ventilation, increased mortality, or increased adverse events
- A highly significant benefit of one group (efficacy) or extreme lack of difference (futility) emerges before the planned end of the study
- Adherence or compliance to study protocol and/or recruitment is well below acceptable goals and the ability of the study to achieve its goals is seriously compromised
- Evidence external to the study renders it unethical to continue the study.

Group sequential monitoring will be used to stop the study if large treatment differences appear before the end of the study and the method of stochastic curtailment will be used to stop the study early if there is little chance of finding a significant difference between groups. An O'Brien-Fleming (154) stopping rule would be used, and the sample size has been adjusted to accommodate three formal interim looks at the primary outcome after approximately 400, 1200, and 1800 of the outcomes have been collected. Monitoring of other aspects of the study, including reports from site visits as they are completed, and recommendations for possible changes in the study protocol will be the prerogative of the Data and Safety Monitoring Board. This will include review of study endpoints and adverse events by the Data and Safety Monitoring Board after study outcomes at these time points, or as requested by the Data and Safety Monitoring Board.

Specific Aim 2: For the economic analyses, we will collect data on resources used by subjects and in protocol implementation from the sites and will multiply resources used by US cost weights. We will also summarize the per patient implementation cost across all sites.

We hypothesize that protocolized sedation decreases costs because, if effective, decreased in-hospital resource use will offset protocol implementation and delivery costs. We will test this hypothesis by comparing differences in hospital costs. These data will be available for all subjects and do not require imputation, but they will be log-transformed to reduce the anticipated skewness. We will also conduct analyses on data truncated at the 95th percentile to mitigate the effect of outliers. We will test for differences using standard nonparametric tests. Because differences in costs may be explained by several factors that may be unequally represented across intervention and control subjects, in secondary analyses, we will construct multiple linear regression models with log-transformed costs as the dependent variable, and treatment assignment (control vs. intervention), age, gender, and PRISM score as covariates. The costs will be calculated per survivor in all patients. In addition, we will calculate total costs and costs per non-survivor.

We will conduct the primary cost-effectiveness analysis from the US societal perspective. To maximize information gained from all sites in the trial, our primary analysis will include cost-streams (based on US cost weights) and clinical outcomes from all sites to generate the strongest estimate of overall treatment effect and to include the same sample in both the numerator (costs) and denominator (effects).

For the Base Case incremental cost-effectiveness ratio (ICER), we will calculate the ratio of incremental costs to incremental effects of protocolized sedation in general over usual care, where the ICER is given by:

$$\mathrm{ICER} = \frac{\mathrm{Cost}^{\mathrm{treatment}} - \mathrm{Cost}^{\mathrm{control}}}{\mathrm{Effect}^{\mathrm{treatment}} - \mathrm{Effect}^{\mathrm{control}}}$$

and costs are the mean subject hospital costs incurred in the intervention and control arms (expressed as Y2012 US$) and effects are the proportion of subjects alive at hospital discharge. We will express ICER as differences in costs and effects ($/survivor).

The development of a Reference Case necessitates estimation of long-term survival and quality-adjusted survival, which is particularly difficult in children, as there is no established method by which to assign utilities to newborns and young children. Therefore, we will determine quality-adjusted survival for the first six months post-discharge in adolescents (children older than 12 years). We and other investigators have assigned utilities to children using comparable adult conditions. (122, 155, 156) We will perform additional exploratory analyses in all subjects assigning subjects living with chronic conditions the average utility of adult patients living with similar chronic illnesses in the Beaver Dam general population cohort. (157) The assignment of quality-adjusted life years (QALYs), even among adults, is a subject of

ongoing investigation. Should a new, more robust approach be developed prior to our study's execution, we will consider incorporating it into our analysis.

We will conduct sensitivity analyses on a range of parameters reflecting our estimates and assumptions regarding treatment effectiveness, long-term and quality-adjusted survival, and short- and long-term costs of care. We will generate one-way sensitivity analyses on all parameters and two-way or multi-way sensitivity analyses on parameters that relate directly to treatment. In our estimation of costs, we will vary the cost weights (from 50% to 200%) for all hospital resource use measures and estimates of implementation costs. We will vary our estimate of physician costs during hospitalization (defined as 17% of hospital costs) from 0% to 25%. In our estimation of effects, we will vary the hazard ratios associated with treatment effect across their 95% CI. In our discounting, we will reset the discount rate (set at 3%) to 0% and to 5% for both costs and effects and to 0% for effects only while keeping costs at 3%. We will present sensitivity analyses as tables and graphs showing the variation of ICER point estimates.

Specific Aim 3: For the post-discharge follow-up study, we will compare the control and intervention groups using chi-square tests and logistic regression for categorical outcomes (PCPC and POPC) and t-tests, linear regression, or Wilcoxon rank-sum tests, as appropriate, for continuous outcomes (Infant Toddler Quality of Life questionnaire, Pediatric Quality of Life Inventory, and Child Posttraumatic Stress Disorder Symptom Scale). We will also examine the relationship between functional status and quality of life, using generalized estimating equations or mixed effects models to account for potential correlations in the outcomes within each center. Similar regression methods as described above will be used to control for variables that are likely to be associated with outcomes. We will also explore whether there are systematic differences in parent vs. child responses. In sensitivity analyses, we will model these differences for children who could not respond.

Reliability and Validity Analyses: Analyses will assess the refined SBS and WAT-1 tools, extending the work done previously. (47, 105) We will assess SBS interrater agreement by comparing the SBS rating (ordinal score of –3 to +2) of each patient between rater pairs and calculating concordance rates (percent of ratings where the two raters agreed exactly) and weighted kappa coefficients. We will examine WAT-1 interrater reliability of overall scale scores (range 0 to 12) by intra-class correlation coefficients calculated using a one-way random effects model, based on all available paired ratings which may include multiple rating occurrences for each patient. To address the issue of intra-cluster correlation among multiple ratings of the same patient, we will also conduct these analyses using only the first rating of each patient or using only a randomly-selected single rating for each patient. To assess the degree to which the SBS and WAT-1 tools measure what they are intended to measure (construct validity), we will conduct analyses to examine the convergence of the SBS and WAT-1 ratings with scores on other measures that are theoretically related to the same concepts (convergent validity) and the ability of the SBS and WAT-1 ratings to differentiate "known groups" (discriminant validity). Specifically, we will compare ratings on the SBS with scores on the Glasgow Coma Scale (GCS), an indicator of the level of consciousness. We will calculate correlation coefficients, compare mean or median GCS scores across SBS levels using ANOVA or the Kruskal-Wallis test, and run proportional odds regression models predicting GCS score using generalized estimating equations to account for intra-cluster correlation due to multiple ratings on an individual patient. We will also conduct longitudinal analyses to assess the degree to which SBS and WAT-1 ratings are sensitive to sedation exposure. All reliability and validity analyses will be conducted stratified by patient age group.

Overall, the primary goal is to compare the duration of mechanical ventilation in the control and intervention groups. Differences between treatment groups will be considered statistically significant if the two-tailed p-value is <0.05. Careful assessment of the results from secondary analyses and outcomes will be made, though no formal multiple comparisons procedures are

planned. Data analyses will be performed using SPSS (SPSS Inc., Chicago, IL) or SAS (SAS Institute, Inc., Cary, NC).

In addition, additional statistical analyses for Specific Aim 1 and Specific Aim 3 will consider whether there is any confounding or effect modification of treatment group differences on the basis of gender and racial/ethnic groups. In particular, we will consider analyses that adjust for gender and racial/ethnic group, and test their possible interaction with treatment group effects. Should any important clinical or statistical differences be found, they will be disseminated in study publications.

E.7.5 Sample Size and Power Considerations

We assume that patients managed per pediatric sedation management protocol will experience a shorter duration of mechanical ventilation than those not managed per sedation protocol. Data from our pilot sedation management study yielded a median length of mechanical ventilation of 141 hours in site 1 and 177 hours in site 2 during their baseline periods. A priori, clinicians determined that a 20% reduction in the duration of mechanical ventilation was clinically important (e.g., going from 141 to 113 hours, or 177 to 142 hours). We base our sample size calculations below on this hypothesized 20% reduction, or hazard ratio of 1.25. This clinically important 20% reduction, or hazard ratio of 1.25, appears to be plausible from the pilot study. Combining data from both pilot sites (114 baseline and 79 intervention subjects), the adjusted hazard ratio was 1.24 (95% CI 0.91-1.67), adjusting for PRISM III score, POPC at enrollment, and study site. To be conservative in case of site drop-out, we base our initial sample size calculations below on having 22 sites participate (7 small, 8 medium, and 7 large PICUs).

Calculations assuming independence: Assuming independent lengths of extubation and proportional hazards between treatment groups, we require 892 total "events" (extubations) for a two-sided 0.05 level log rank test to achieve 90% power to detect a 20% reduction in the intervention group, compared to the control group, assuming three interim analyses for efficacy or futility after approximately 16%, 49%, and 74% of the study outcomes have been collected (East, Version 5.3, Cytel Statistical Software, Cambridge, MA). This corresponds to a hazard ratio of 1.25. We expect no more than 15% of the subjects to be censored (either because the subject was still intubated on day 28, or had died prior to day 28 and had not remained extubated for >24 hours prior to death), given our prior experience with the prone positioning study and the pilot sedation management study. Thus, we require 892 / (1–0.15) = 1050 total enrolled subjects in the study to achieve this power. This study size of 1050 enrolled subjects also has 80% power to detect an 18% reduction in length of extubation (hazard ratio = 1.22), and 75% power to detect a 17% reduction (hazard ratio = 1.20). Thus, we expect to have sufficient power to detect a clinically important reduction in the length of extubation in the intervention group.

Calculations assuming non-independence: The above sample size calculations assume that we have independent samples. As this assumption may be violated because subjects from the same site may be correlated, we calculate another sample size estimate, taking into account the intra-cluster correlation coefficient (ICC). The sample size inflation factor, or design effect, needed is (1 + (m–1) x ICC), where m is the average cluster (site) size (arithmetic mean). (158, 159) Our experience in the prone positioning study (90) and the pilot sedation management study suggests that the within-site variability in clinical outcomes was much larger than the between-site variability, yielding a negligible correlation between subjects from the same site. The ICC for the martingale residuals for extubation times was estimated to be 0.00 in the seven-site prone study, and 0.01 in the two-site pilot sedation management study. Conservatively based on the 22 sites from the first batch, using ICC = 0.01 leads to m = 90.4, or 22 x m = 1990 total subjects needed, giving 90% power to detect a 20% reduction with a design effect = 1.89.

With cluster-randomized designs, increasing the number of sites leads to lower design effects, so there can be increased power (with the same total sample size) or decreased sample sizes

needed (for the same power). Starting with the same calculations above assuming independence (requiring 1050 total enrolled subjects for 90% power), using 26 sites leads to m = 67.1 or 26 × m = 1746 total subjects needed with a design effect of 1.66. Using 28 sites leads to m = 59.4 or 28 × m = 1664 total subjects needed with a design effect of 1.58. Using 30 sites leads to m = 53.3 or 30 × m = 1600 total subjects needed with a design effect of 1.52.

The above design effect calculations are based on equal cluster sizes across all sites. Eldridge et al. (139) showed that, for small to moderate ICCs, the effect of adjustment for variable cluster size on sample size estimates is negligible. However, Hayes and Moulton (147) suggest that a simple modification can be made to the design effect to accommodate varying cluster sizes. In particular, we now use m to denote the harmonic mean of the cluster sizes (rather than the arithmetic mean), which tends to yield slightly higher design effects. The harmonic mean of the cluster sizes is not known in advance. We choose 2448 enrolled subjects as our target sample size, giving 90% power to detect a 20% reduction in length of extubation controlling for censoring, three formal interim analyses for early stopping, modest within-site correlations, as well as moderate site-to-site variability in cluster sizes (by inflating the design effect by a range of 23% for 22 sites to 53% for 30 sites). Also, Zou et al. (141) showed that standard group sequential methods can be applied to cluster randomized trials when interim analyses are warranted, in the context of binary outcomes. We will carefully ascertain the appropriateness of interim analyses for clustered survival outcomes, but we anticipate that standard group sequential methods will also be valid in this case.

Adequacy of the study population: In preparation for this study, Dr. Curley required each participating center to screen their PICU for one month using the pilot study screening forms, and found approximately 190 eligible study subjects in the participating centers. In our pilot sedation management study, 6% of parents approached for consent refused participation or were unable to provide consent. Even with up to a 46% refusal rate or lower than expected enrollment (compared to 190/month), we expected to enroll a minimum of 190 x 0.54 = 102 patients per month. When study enrollment rates were reviewed in June 2010, they were slightly lower than expected above. To increase enrollment rates, we will add additional sites in a second batch in 2010. Our inclusion of approximately 26 centers (instead of 22) provides additional assurance of achieving enrollment goals.

Detectible effects for post-discharge outcomes: Quality of life and emotional health assessments will be made on a stratified random sample of subjects enrolled in the trial (excluding the baseline period). The sample will be stratified by age (<2, 2-4, 5-7, 8-12 years, and 13-18 years, as per instruments used) and site. Conservatively assuming 18 sites participate, the trial will enroll an average of 2448/18 = 136 patients per site (range 72-216 per site). Assuming 10% in-hospital mortality, an average of 122 subjects (range 65-194 per site) will be eligible for follow-up at each site. We will attempt to follow half of these subjects (average of 61 per site, range 33-97 per site). Assuming an 18% loss to follow-up, we expect to contact an average of 50 subjects per site (a minimum of 900 subjects in all, range 27-80 per site). Effect sizes were computed using a two-sided 0.05 level test, a power of 80%, and a t-test comparing control vs. intervention groups that adjusts for clustering, similar to above. With 900 subjects, the detectible effect is 0.14 standard deviations (effect size) when the ICC = 0.002, 0.17 when ICC = 0.01, and 0.21 when ICC = 0.03. Some analyses will involve age-specific quality of life measures (Infant Toddler Quality of Life questionnaire, Pediatric Quality of Life Inventory), each being administered to approximately half the cohort. With 450 subjects (average of 25 per site, range 14-40 per site), the detectible effect is 0.20 standard deviations when the ICC = 0.002, 0.21 when ICC = 0.01, and 0.25 when ICC = 0.03. Thus, we have high power to detect small to moderate differences between treatment groups in the group as a whole and for age-specific measures. For example, for the Pediatric Quality of Life Inventory, which has a scale from 1 to 100 and a population mean of 83 and standard deviation of 13 in control populations, the study will be powered to detect treatment group differences of 3 or more

points. With approximately 26 sites (instead of conservatively assuming 18), the detectible effects for post-discharge outcomes with 900 subjects will be even smaller.

If our loss to follow-up rate is unexpectedly high, we will randomly select additional subjects from the pool of survivors to follow to ensure that the follow-up sample size will be adequate. In addition, if an adequate rate of interview completion is accompanied by an unexpectedly low rate of return for the standardized instruments, we will consider telephone administration of the instruments. We will also compare demographic and clinical characteristics of contacted subjects with those who were lost to follow-up (and with subjects whom we did not attempt to contact) to ensure that the follow-up cohort was representative of the trial as a whole. Overall, the study is adequately powered to determine the safety of *RESTORE* in terms of post-discharge outcomes.

E.7.6 Dissemination Plan and Data Archiving

The results of this clinical trial will be critically important to disseminate to critical care clinicians, both pediatric and adult. In the final two years of the study the Steering Committee will develop the strategic plan for the comprehensive presentation and publication of the study findings. Dissemination will begin after the intervention periods have been completed and analyzed for all sites. The DCC will assist Dr. Curley and Steering Committee members to prepare abstracts and papers for presentation at the annual meetings of American Thoracic Society (ATS), Critical Care Medicine (CCM), American Association of Critical Care Nurses (AACN), the European Society of Pediatric and Neonatal Intensive Care (ESPNIC), and American Society of Health-Systems Pharmacists (ASHP). Dr. Curley will provide the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) network an update on the clinical trial twice yearly to maintain disciplinary interest in the study. It is anticipated that the results of this study will impact the professional training of numerous disciplines and will inform clinicians on the long-term state of health of PICU survivors. In addition to several primary publications targeted at high priority journals, we anticipate numerous secondary publications in the medical, nursing, and pharmacy journals. Final data sets and statistical analyses will be archived for safe-keeping.

E.8 Data Management and Quality Control

The Statistics and Data Coordinating Center of the Department of Cardiology at Children's Hospital Boston will manage the data for the main study. Data for the follow-up study on post-discharge quality of life will be managed by the CRISMA Center at the University of Pittsburgh.

E.8.1 Data Management System

Children's Hospital Boston uses a Web-based Data Management System (DMS) for clinical research. The DMS can support a variety of features including Web-based data capture, lab data management, and protocol tracking. The system provides a hierarchical view of each study participant, which allows study staff to manage eCRFs as defined by the clinical protocol. Forms have been designed so that the triggers and expectations for the eCRFs can be modified as needed for each patient. Many cross-form validations will be programmed to ensure data quality.

The data entry component validates user responses based on specified range checks, executes skip patterns, and resolves outlier responses through an integrated annotation dialog. The system supports a complete audit trail of transactions to ensure data integrity and regulatory compliance. Furthermore, the system provides staff with a variety of reports to assist project management and study data may be readily exported for use with Microsoft Excel, SPSS, SAS, or other software.

E.8.2 Data Coordination

In addition to standard data management reports, the DMS is programmed with custom reports including subject accrual and summary worksheets, to assist DCC and clinical center research staff in managing daily study operations. The DMS will perform data checks of all fields for valid ranges and completeness of data and will provide an audit trail of the edit resolution process.

This includes the all previously and currently entered values, the programmed acceptable range for the value, a place to record verification or correction, and the identity of site personnel who entered or edited the data value. The DMS will track and identify for each subject the study forms that are expected but not yet entered into the DMS. All site personnel will have the ability to run, at any time, reports that will provide detailed lists of expected forms and of all data queries by patient for their site. In addition, the DCC will provide these reports to site coinvestigators, as needed, to ensure timely submission of data forms and resolution of data queries.

E.8.3 Data Entry, Editing, and Audit Trails

All CRF data will be entered into the web-based DMS by clinical site personnel to ensure accurate record keeping. As subject data are entered into the system, the DMS identifies and tracks the pertinent study events and eCRFs. Context-specific help and range and logic checks reduce the number of errors and assist the data entry process. When appropriate, skip patterns are specified to ensure accurate data entry. The DMS contains a complete audit trail of all original values and all edits. All missing values and data discrepancies are tracked by the DMS and may be reported to study staff. During data entry, each value entered is subjected to a variety of quality control checks including range checking, table look-up for value accuracy, intra- and inter-form logical consistency checks, and context-specific help messages for data coding.

When an error occurs, the system notifies the user and explains the nature of the error by means of a pop-up help screen. The help screen displays the question and the range of valid responses. The help screen may also reference responses to other related questions that make the current entry invalid. At this point, the system user may correct a data entry error, confirm an out of range value, or temporarily bypass the error.

E.8.4 Data Quality Control/Assurance

All eCRFs will undergo 100% data audit (against the medical record) at the clinical sites before data entry. The data audit includes visual screening for missing data and inconsistencies. During data entry at the sites, the DMS will generate a list of open queries for all out of range values, inconsistencies, and missing data and send to the site for resolution. To reduce data entry errors, a specified selection of variables for a 10% random sample of all patients will be double checked by the sites using the source verification capabilities of the DMS. Any discrepancies will be reviewed and resolved by the Data Manager and used for re-training, as needed. In addition, routine monthly and ad hoc reports will be run as part of quality control and assurance. The reports will track patient accrual, patient status, protocol deviations, completeness of data, and responses to data queries. The DCC Director, Project Manager, and Data Manager will review all reports monthly with a view to improving or maintaining high performance.

E.8.5 Data Confidentiality, Security and Back-up

To ensure data safety and reliability, server back-up procedures will be executed daily to back up all electronic study related materials, which include database, Word documents, statistical programs, and files. Access to the DMS is strictly prohibited and requires user authentication. Authorized users include data-entry personnel at each site, site Study Coordinator, the DCC PI, Project Manager, Data Manager, Data Coordinator, the database programmer, and biostatisticians. Any hard copies of eCRFs with subject ID codes will be stored in locked file cabinets at the clinical sites, accessible by authorized staff only. Identifiable subject data, such as contact information and medical record numbers, will be stored separately and securely at the clinical sites, away from the DCC.

E.8.6 Firewalls

All application software and data will be hosted securely on the Children's Hospital Boston (CHB) network. The CHB network is protected by several firewalls and security is monitored and

audited regularly by the CHB Information Services Department (ISD). All application and database software will enforce access rules through user authentication and authorization schemes established by the DCC and ISD. The DCC will ensure that no data are compromised or shared inappropriately by maintaining strict security procedures between personnel, data, and all other study investigators. For example, Dr. Curley and her research staff will have access to status reports within the database, but they will be unable to view or change any of the study participant data.

E.8.7 Site Visits

The DCC will coordinate site visits. A study monitor (pediatric critical care nurse with research experience) will conduct site visits at the PICUs randomized to receive the intervention at least 6 months after the start of the intervention phase of the trial. The review will include an observation during multidisciplinary rounds, spot check of interrater reliability on SBS and WAT-1 scoring, examination of all study procedures and procedures to resolve queries, and an audit of at least 10% of the eCRFs randomly selected by the DCC. Retraining will be provided as necessary. A specific site visit checklist will be used and a report generated after completion of the visit. Members of the Steering Committee and DSMB will review these reports. The site coinvestigators will be responsible for correcting deficiencies, if any, to the satisfaction of the Steering Committee and DSMB members (majority vote). A study monitor will also conduct site visits at the PICUs randomized to provide usual care at least 6 months after the start of the control phase of the trial, to spot check interrater reliability on SBS and WAT-1 scoring and to audit data collection.

E.8.8 Data Management for the Follow-up Study

The CRISMA PI, Dr. Watson, and biostatistician, Dr. Kong, will oversee all aspects of the follow-up data collection and analysis. Dr. Watson and the CRISMA Project Manager will oversee coordination with the DCC and study sites, as well as data collection and monitoring. Dr. Kong and the CRISMA Data Manager will lead the performance of tasks that are required for maintenance of the database and to insure accuracy and consistency of the database used in this project. Dr. Kong will communicate with the CRISMA Data Manager's team frequently with regard to specific tasks to be performed, with ongoing issues discussed and updated in a more general fashion at project meetings. Regular weekly project meetings will be held to ensure that all aspects of the project are progressing optimally.

Confidentiality: At no time will CRISMA reveal subject identities in any description or publication of the research for scientific purposes. All data obtained with subject or provider identifiers will be kept in locked file cabinets and in password protected computer files to ensure confidentiality, and all paper file contents will be shredded before disposal. All subjects will be assigned a unique study number for use in the computer database. In addition, all research personnel are required to review and sign CRISMA's Data Confidentiality Policy. By signing this form, study personnel take a further step toward committing to protect patient confidentiality and study information.

Manual of operations and procedures: Standard operating procedures (SOPs) will be written and study forms developed in adherence to guidelines approved by CRISMA and blanketed across all projects. The CRISMA PI, Dr. Watson, and the CRISMA Project Manager will review all study-specific materials, using a sign-off form to insure that approval is gained prior to implementation of said form or operating procedure. A CRISMA study Manual Of Operations and Procedures (MOOP) will be compiled and available to all members of the study team. It will include a listing of site personnel, follow-up protocol and current IRB approval letter for each site, SOPs, all approved forms as well as dates and reasons for revisions of said form, copies of the tracking and other data reports discussed during the various meetings or minutes that record important information from these reports, and progress reports. Current materials will always be housed in the MOOP, with outdated forms or past versions of SOPs maintained in secure file cabinets. All SOPs will be written by study personnel with the highest level of

expertise in the area of the protocol to be written, in adherence to guidelines approved by CRISMA and blanketed across all projects.

Data storage, security, and tracking: Data management at CRISMA will follow the policies and procedures established in our prior multicenter follow-up studies and will be coordinated by Dr. Kong. The data management system will be based on a PC platform, a database server (Microsoft Access, SQL Server 7), and Microsoft Visual Basic. Differential backups of the server are made every weekday and complete backups monthly.

At hospital discharge, site coordinators will forward to CRISMA signed consent/assent forms for subjects consenting to follow-up, along with subject demographic and contact information. Information will be sent via secure FAX or encrypted e-mail. The FAX machine at CRISMA is in a secure area with access restricted to research personnel. Each paper Data Collection Form (DCF) will be identified by the corresponding study ID number and enrollment date. Data from the paper DCF will then be entered and uploaded to the study database server and used to categorize subjects based on stratification criteria (site and age group). From each group, one-half of consenting subjects will be randomly selected for follow-up, and selected subjects will be added to the Subject Tracking System. This system is based on a contact management software program, ACT!®, and prompts research staff at the appropriate time to conduct the follow-up interview. Completed paper copies of DCFs will be locked in a secure file cabinet. All other paper records will also be kept in locked file cabinets, and electronic records will be stored on a secure, password-protected file server.

Data quality and auditing: Data management will follow policies and procedures established in our prior multicenter follow-up studies and will produce new SOPs as needed to standardize all data management processes. Other data quality assurance measures include interface self-checks consisting of embedded codes in data entry interfaces to prevent unexpected entries from taking place. In addition to routine data auditing (described below), each data-entered DCF will be verified at least once. Data documentation (data dictionary, data acceptance criteria, calculated variable algorithms, rationale and codes, etc.) and data cleaning procedures (automated SQL queries that will scan the data tables for consistency and compliance with their acceptance criteria, see below) will be routinely employed.

All personnel will be trained and audited to ensure compliance with protocol performance, including data handling and tracking procedures, and reports will be generated weekly. Data will be audited during the data collection period. It will consist of a set of predetermined SQL queries that will be run against the database to check for the data consistency and compliance with the appropriate quality criteria. This audit will involve a team of personnel led by the CRISMA Data Manager seeking to solve and document any inconsistencies and errors found with the queries and in the process of comparing the unexpected entries with the corresponding paper DCF records. In addition, independent re-entry of a minimum of 10% of DCFs will be performed.

Data reporting and monitoring: CRISMA will monitor subject enrollment and follow-up rates. The CRISMA Data Manager will generate weekly reports, which include number of contacts and number enrolled. These reports will be used to compile a quarterly status report to provide valuable information at-a-glance as to cohort characteristics. All reports will be stripped of identifying information other than study ID number. The variable codes and their measurement, as well as derived variables, will be documented in codebooks. As the follow-up evaluations progress, the codebook contents will expand. Once the database had been cleaned, the CRISMA Data Manager will generate appropriate datasets in response to the specific needs of the proposed analysis. These datasets will be provided together with a descriptive statistical analysis of the relevant variables.

E.8.9 Quality Control of Telephone Questionnaires

The CRISMA center has been performing quality control of telephone questionnaires and has standard operating procedures regarding their administration. We anticipate using no more than

two telephone interviewers for all interviews, and interviews will be conducted following standard methods. Mock interviews will be performed and evaluated during interviewer training to ensure consistency between interviewers. We will allow a two-month time window (one month before and one month after the 6 month time point). We will mail a summary of the interview questionnaire to the child's parents before calling. We will enter data electronically within one month using standard data entry checks and routine data quality auditing.

E.9 Quality Control Procedures

E.9.1 Development of Case Report Forms and Manual of Operations

The DCC has extensive experience in the design of Case Report Forms (CRFs) and preparation of Manuals of Operations (MOOs). DCC staff will assist Dr. Curley in eCRF and MOO refinement to ensure the highest possible data quality. Forms design features include the selection of valid, reliable measurements that are least burdensome, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open ended questions), smooth flow (clear skip patterns) to reduce missing data, and ensuring that measurement units are consistent across all sites. The detailed MOO will ensure efficient and accurate data collection, ease of communication, and will allow MOO updating, as needed, including dated footers. Members of the Steering Committee will sign off on eCRFs and the MOO before implementation. The eCRFs for this study are based on those used successfully in the pilot sedation management study. We have made appropriate revisions based on our experience.

E.9.2 Training, retraining, and certification

Site coinvestigators will be trained in data collection methods by the DCC Project and Data Managers prior to enrolling patients. The site coinvestigators will be trained to collect data using the eCRFs. They may then delegate data collection to a research assistant. The MOO describing SOP for data collection will ensure consistent decision-making across centers. These procedures will be evaluated during study site visits.

After baseline training is provided, each nurse coinvestigator will provide 5 sets of paired SBS and WAT-1 ratings. These 100 paired scores (5 per site) will be evaluated for interrater reliability and maintained at greater than 90%. If interrater reliability is below 90%, coinvestigators will be asked to review training materials and resubmit paired ratings.

Site Coinvestigator Training (randomized to intervention): Since consistent application of *RESTORE* is critical to the conduct of the study, site coinvestigators randomized to the intervention arm will be required to attend a start-up meeting and undergo a competency-based training program and certification process prior to enrolling intervention patients. Study personnel will be required to review the Manual of Operations, view the study videos and complete and pass a scenario-based post-test.

Clinical Team Training (randomized to intervention): A critical component of the intervention is an educational model that can be implemented through traditional or web-based teaching methods. We will implement common (applies to all intervention PICUs) and specific (tailored to a specific PICU needs) strategies to overcome barriers to protocol implementation using the conceptual model for barriers to guideline implementation. (76) Building upon our pilot experiences, *RESTORE* training will be multifaceted and include all clinicians (physicians, nurses, clinical pharmacist and physicians-in-training) involved in the comfort management of intubated mechanically ventilated patients. A multidisciplinary, cooperative approach is necessary to assure compliance and successful implementation of protocols. Training material will include a discipline-specific slide package, informal case discussions, videotape on the Nurse-Implemented Goal-Directed Comfort Algorithm and arousal assessment, pocket reminder cards, and bedside booklets. Physician and pharmacist training will focus on identifying the patient's trajectory of illness, collaborating with nursing in prescribing the daily sedation goal, and completion of the standardized order template. Nurse training will likewise focus on

sedation and withdrawal scoring, trajectory analysis and collaboration but also will include practical support on the daily arousal assessment and titration of sedatives. Respiratory therapists will also require training on the ERT. Prior to the intervention phase, all physicians, physician-in-training, unit-based clinical pharmacist, charge nurses and nursing staff will be required to document their understanding of the intervention by completion of a discipline-specific scenario-based self-assessment evaluation. Champions will receive the above plus an in-depth presentation on the background of the study, review of the algorithm, and study procedures. Experienced coinvestigators (Gedeit and Soetenga) will also be available to assist clinical teams implement the protocol within their practice settings. Training time will be tracked so that protocol burden can be described during dissemination.

To maintain minimal competency in study procedures, sites will be required to enroll a minimal number of patients per month. If enrollment drops under the minimum number of patients enrolled per month (1: small PICU; 2: medium PICU; 3: large PICU) for 3 consecutive months the site will be asked to implement a quality improvement (QI) plan to include physician and nurse retraining. If the site enrollment continues to be low after implementation of the QI plan then the Principal Investigator will ask the Steering Committee for a recommendation on continued site participation.

E.10 Study Organization

E.10.1 Clinical Centers

Each site will have a physician, site advanced practice nurse, and clinical pharmacist coinvestigator. In the intervention PICUs, this triad will be responsible for discipline specific education, compliance assessment and re-teaching. Research assistants will be responsible for screening and completion of eCRFs. Site coinvestigators are responsible for the accuracy of the eCRFs and for their timely submission to the DCC as described in the MOO.

E.10.2 Data Coordinating Center

The Statistics and Data Coordinating Center of the Department of Cardiology at Children' Hospital Boston will function as the independent DCC. The Principal Investigator (Dr. Curley) and the DCC Principal Investigator (Dr. Wypij) have a successful history of working together but also separately, when required, during the prone positioning clinical trial and the sedation management pilot study. The Principal Investigator will conference call every month with the DCC to discuss issues related to data quality and integrity.

E.10.3 Study Committees

E.10.3.1 Steering Committee

The Steering Committee, composed of Dr. Curley (Principal Investigator and Chair), core coinvestigators (non voting), Dr. Wypij (Principal Investigator, DCC), one coinvestigator from each clinical site, and the NIH Project Officer (non voting) will serve as the primary decision making body for the clinical trial. The committee members will be responsible for execution of the study design and for its accurate conduct at each site. The committee will meet separately with control and intervention sites by conference call every other month and members will oversee day-to-day operations including adequacy of enrollment, data collection, quality control procedures and overall performance. The standing agenda for the intervention sites will include [1] enrollment data; [2] operational issues; [3] protocol issues including protocol deviations; [4] quality monitoring; [5] safety and adverse event data; and [6] DCC update. The standing agenda for the control sites will include all of these items except [3]. The Committee will review safety and adverse event data and report any concerns to the DSMB. The DCC will prepare reports on recruitment, compliance, data quality, and safety and adverse event data for Steering Committee's review.

E.10.3.2 Operations Committee

The Operations Committee, composed of Dr. Curley (Principal Investigator and Chair), Dr. Wypij (DCC Principal Investigator), the Project Managers, and the Data Manager, will review problems

and issues related to day-to-day management of the study. The committee will meet by conference call at least every other month and the standing agenda will include: [1] review of the time-line; [2] screening reports; [3] site performance reports; [4] DCC report; and [5] overall performance. The Principal Investigator will summarize issues that are reported directly to her and their resolution. The DCC will prepare reports including status reports from each site, screening, enrollment and compliance reports, data quality reports, and adverse events for the Operations Committee's review.
The DCC will also work with each clinical center to ensure:

- Timely submission of data forms and resolution of all data queries
- Training and certification is obtained by all new staff
- Protocol and forms related questions are answered in a timely manner.

E.10.3.3 Coordination of Data and Safety Monitoring Board Meetings

The DCC will prepare and distribute prior to the meetings a written report that provides updates on overall status of the study and summarizes adverse events and key outcome variables, and support other requests from DSMB.

E.10.3.4 Coordination with University of Pittsburgh for the Follow-up Study

The follow-up study on post-discharge outcomes will be conducted by the research team at the CRISMA Center at the University of Pittsburgh. CRISMA will also be responsible for data management and statistical analyses related to these outcomes. The DCC will notify CRISMA monthly of subjects consenting to follow-up. The DCC will also transfer relevant clinical variables to the Pittsburgh team at the close of the study. Research staff conducting the interviews at CRISMA will remain blind to which patients received protocolized sedation (i.e., cluster randomization of sites) during the conduct of the follow-up evaluations.

E.11 Anticipated Problems and Solutions

E.11.1 Enrollment less than predicted; Narrow enrollment window (<24 hours) and imbalance in consent rates between control and intervention PICUs.

Each PICU is expected to screen their PICU daily and enter their screening data into the *RESTORE* database each week. The Principal Investigator will monitor these data and problem solve lower than expected enrollment rates with the site investigators. The Steering Committee will review screening data as a standing conference call agenda item. The narrow enrollment window is expected to impact the control and intervention groups in a similar way. We will monitor refusal rates and have no reason to believe that the enrollment differences between the two groups will collectively differ by 10%. We have a provision for capping over-enrolling centers at three times their group's average monthly enrollment.

In the R21 pilot study, CHWisc required consent for data collection and only 6% of parents/ legal guardians refused or were unavailable to consent. We originally powered the RESTORE study for up to a 40% refusal rate in 18 sites and identified three back up sites. We will now use approximately 26 sites. The power calculation will accommodate a 6-46% parent refusal rate.

The PALISI network will assist the investigative team in problem-solving enrollment issues twice a year. Low enrollment is unlikely since each participating PICU mock screened their units for one month and provided data to support their anticipated enrollment. The control and intervention enrollment periods are at the same time, so we can lengthen, if necessary, the duration of data collection and not imbalance the control/intervention timeline.

E.11.2 Non-compliance with the study protocol

The protocol is designed to provide clinicians with an analytical framework for the evaluation and management of pain and agitation in critically ill infants and children. This protocol is not intended to establish a protocol for all patients supported on mechanical ventilation, nor is it intended to replace a clinician's clinical judgment. It is understood that some patients will not fit the clinical conditions delineated by the protocol and that the recommendations contained in this

protocol should not be considered inclusive of all proper methods or exclusive of other methods of care reasonably directed to obtaining the patient's comfort. Clinicians are expected to deviate from the protocol when they are concerned about patient safety and comfort but all protocol deviations will be evaluated by the site coinvestigators. These evaluations include documentation of the rationale for the protocol deviation (PD) and the follow-up action taken. The Principal Investigator will monitor the monthly PD reports for trends and will contact site investigators when increases in trackable deviations are noted. The Steering Committee will also review quarterly PD reports as a standing conference call agenda item.

We will also determine whether varying levels of protocol compliance results in different clinical outcomes. Perhaps elements of the pediatric sedation management protocol (e.g., setting a daily goal or the immediate titration of therapy by nurses) are more important than others. Knowing this information is important for knowledge dissemination.

E.11.3 Protocol Failure

During the acute phase of illness, some patients may fail to achieve the prescribed level of sedation on the study management protocol. After the physiological etiology is considered (e.g., hypoxia, encephalopathy, etc), physicians may elect to prescribe a third agent to the patient's sedation regimen, e.g., a barbiturate. Additionally, the protocol was not designed to manage patients with delirium who may benefit from an antipsychotic agent. Use of non-study analgesics/sedatives are considered a PD and are tracked by the coinvestigators daily using the walk-rounds form during the intervention phase. Finally, clinicians may choose to remove any patient from the sedation protocol at any time. The rationale for all patient withdrawals will be tracked and discussed by the Steering Committee. Withdrawn patients will be included in an intention-to-treat analysis.

E.11.4 Development of New Sedatives

Although the science of pediatric critical care continues to evolve, it is possible that a new pain or sedation scale will be developed or a new sedative agent will be approved for use in the PICU population in the next six years. Even in the unlikely event that this occurs, this study will provide important data on the effects of a novel intervention that integrates the patient's overall sedation plan of care (needs, goals, and administration) independent of the particular medications used. All advances in the field will be reviewed by the Steering Committee and recommendations for protocol changes must be approved by the DSMB.

E.11.5 Unblinded Assessment

Inclusion and exclusion criteria and outcome variables are designed to be as objective as possible. However, staff at the University of Pittsburgh completing post-discharge quality of life and emotional health assessments will be blinded to treatment assignment and the cluster randomized design during the evaluation.

E.11.6 Impact of the timing of extubation on the sensitivity of the primary outcome variable

During the pediatric prone study (90) only 15% of the patients enrolled were extubated between the hours of 18:00-07:00. This tendency to extubate patients only during the daytime is expected to affect both groups equally so should not bias treatment group comparisons. The exact timing of the ERT can vary as long as ERT results are available for multidisciplinary rounds. Calculating the duration of mechanical ventilation in hours may be more sensitive in detecting differences between treatment groups. Our sample size is large enough to detect a clinically significant one day difference in the duration of mechanical ventilation.

E.11.7 Impact of changes in pediatric critical care management over time on the outcome variables

The impact of changes in pediatric critical care management is expected to affect both groups equally so should not bias treatment group comparisons. Including approximately 26 PICUs will

decrease the duration of the study to the shortest time possible that would still allow a change in practice to be evaluated.

E.11.8 Impact of selection bias in cluster randomized trials

In a cluster randomized trial, allocation of treatment is predetermined so that the potential for selection bias is high. (91) To address this issue we have developed explicit inclusion and exclusion criteria. Each PICU is expected to screen their PICU daily and enter their screening data into the *RESTORE* database each week. Screening data will be audited during site visits.

F. HUMAN SUBJECTS RESEARCH

This Human Subjects Research is an NIH-Defined Phase III Clinical Trial.

F.1 Risks to the Subjects

F.1.a Human Subjects Involvement and Characteristics

Approximately 26 PICUs are collaborating in this study designed to test the effect of a pediatric sedation management protocol on the duration of mechanical ventilation in pediatric patients supported on mechanical ventilation for acute respiratory failure. The approximately 26 PICUs will enroll 2900 critically ill infants and children ≥ 2 weeks of age (and ≥ 42 weeks post menstrual age) and <18 years of age. All baseline and control subjects will receive usual PICU care. All intervention patients will receive the pediatric sedation management protocol as described in Section E.3.2. From the subject's perspective, this includes team agreement on their sedatives, a daily assessment of their sedation needs, prescription of a daily sedation goal, and titration of their sedatives to achieve the prescribed goal.

The parents/legal guardians of a stratified random sample of subjects will be invited to participate in a follow-up assessment scheduled at their convenience 6 months after their child's PICU discharge. The purpose of the assessment is to assess the child's long-term quality of life and psychologic sequelae, and post-discharge resource use. All interviews will be conducted by trained personnel from the University of Pittsburgh in either English or Spanish. There are no expected risks associated with the follow-up study aside from the time burden imposed on the subjects and their families by the questionnaires and the structured telephone interviews. We anticipate that the interview will be completed in 7 to 20 minutes, depending on whether we speak only to the parent/legal guardian or also to the child subject.

F.1.b Sources of Materials

Sources of research material will include data normally contained within the subject's medical record. Each site will maintain an enrollment log that will link each patient to a unique study number. All data collection forms will contain this unique study number. The paper enrollment logs and any paper version of the eCRF will be maintained in a locked filing cabinet. All data received at the DCC will be de-identified. To ensure regulatory compliance, paper enrollment logs will be destroyed 6 years after the completion of data analysis.

The follow-up interview data will be collected specifically for this research project and will occur only with parental/legal guardian consent and subject assent (and consent from subjects turning 18 after PICU hospitalization). All primary and secondary subject data will be received by a dedicated secure fax machine, by US Mail or secure website (for return questionnaires) or by telephone with secured data entry. All data will be secured for the purpose of confidentiality, and data will be used only for research purposes.

F.1.c Potential Risks

Potential risks associated with the use of analgesics and sedatives and their titration include inadequate pain management, inadequate sedation management (over sedation and agitation), clinically significant iatrogenic withdrawal symptoms, unplanned extubation, airway irritation from movement of the endotracheal tube within the airway, extubation failure/reintubation within 24 hours of extubation, dislodgement of vascular access or drainage tubes, VAP, CA-BSI, and stage 2+ pressure ulcers.

Site coinvestigators will report unanticipated, related or possibly related problems to their internal IRBs, the DCC and Dr. Curley within 24 hours. Dr Curley and local coinvestigators will immediately follow up on these problems and communicate with the DSMB and external IRBs per NIH guidelines. Site coinvestigators will report all SAEs to the DCC within 24 hours. All serious, unexpected adverse events that are possibly, probably or definitely related to the intervention will also be reported to Dr. Curley within 24 hours. Dr. Curley and local coinvestigators will immediately follow up on these SAEs and communicate with the DSMB and external IRBs per NIH guidelines. All adverse events will be reviewed monthly for trends. Non serious adverse events will be submitted to the DSMB twice yearly. If aspects of clinical care are identified as preventative to iatrogenic injury, they will be implemented for study patients from that point forward. Potential risks associated with study participation also include the loss of confidentiality.

Risks associated with the follow-up part of this study are related to potential loss or release of confidential information. Each consenting parent/legal guardian will provide identifying and contact information, allow review of his/her child's hospital records, and provide information about his/her child's health status, functional status, health-related quality of life, and emotional status. These risks, and the steps enacted to protect against these risks, will be specified in the parental/legal guardian consent forms, all of which will be HIPAA-compliant.

Parents/legal guardians may feel psychological distress during the collection of follow-up data. Parents/legal guardians will be reminded at the start of the interview that they can stop the interview at any time. At the end of the interview, parents/legal guardians will be specifically asked if they would like to have further conversations with their child's primary intensive care physician. If they would, they will be provided with the phone number of the ICU physician's office, and CRISMA staff will also notify the site coinvestigator directly that a subject or subject's family member desires additional contact.

F.2 Adequacy of Protection against Risks

F.2.a Recruitment and informed consent

Site coinvestigators or their designee will screen for potential subjects each day using the patient screening logs. Patient eligibility for enrollment will be determined after a complete review of the patient's demographic and clinical information. Screening logs will note the rationale for non-enrollment (for example, exclusion criteria, parent/legal guardian unavailable/unable to provide consent, consent refused, missed enrollment window). Screening data, without identifying information, will be entered into the web-based data entry system each week. We will collect HIPAA-compliant minimal data on all patients who meet study criteria but are not enrolled; specifically, age in months, gender, race, ethnicity, primary reason for intubation. These data will allow the research team to compare enrolled patients to non-enrolled patients and respond to any potential enrollment bias. Particular attention will be paid to gender and minority representation to ensure that the proportion of female and minority children enrolled in the study is similar to the population who are screened and found to meet eligibility criteria in each site.

After verifying the patient's eligibility status with the care team, the site coinvestigator (or their designee) will inform the parent/legal guardian that their PICU is participating in a multicenter study of sedation practices and is seeking their informed consent for study participation. One of three parent/legal guardian consents will be presented to the parent/legal guardian: baseline, control, or intervention group (see Appendix I.A, I.B and I.C).

Each consent explains that the purpose of the research is to evaluate the safety and effectiveness of an experimental pediatric sedation management protocol for managing pediatric patients with acute respiratory failure managed in comparison with usual care; describes the cluster randomized design of the study and describes the study procedures used

to manage sedation in each group of subjects; describes all foreseeable risks and discomforts and describes any expected benefit.

- During the baseline data collection phase, the parent/legal guardian will be asked permission for data collection.
- In the control group PICU, the parent/legal guardian will be asked permission for data collection and will be invited to participate in the follow-up aspect of the study.
- In the intervention group PICU, the parent/legal guardian will be asked their permission to use the pediatric sedation management protocol to manage their child's sedation and will be invited to participate in the follow-up aspect of the study.

The RESTORE intervention will only be applied as a research protocol in patients whose parent/legal guardian give permission for their child to participate in the research. Specifically,

- Team education (i.e., physicians, nurse practitioners, bedside nurses, respiratory therapists, and clinical pharmacists) and consensus on the use of sedatives in pediatric patients with respiratory failure supported on mechanical ventilation; specifically, our educational plan will be presented as a research protocol.
- Team identification of the patient's trajectory of illness and daily prescription of a sedation goal; specifically, in enrolled patients.
- Nurse-Implemented Goal-Directed Comfort Algorithm that guides moment-to-moment titration of opioids and benzodiazepines; specifically, in enrolled patients.
- Team feedback on sedation management performance; specifically, walk rounds and feedback on enrolled patients.

No recommendations regarding sedation management will be made (1) before consent or (2) in patients whose parent/legal guardian refuses consent. In these cases sedation management will be left entirely to the bedside team.

Parents/legal guardians will be approached and asked to provide consent within 24 hours of meeting study criteria. Enrolling patients within 24 hours of intubation will allow the site coinvestigator to work closely with the care team to approach the parent/legal guardian at a time that would not significantly overburden them and allow the parent/legal guardian sufficient time to consider their participation. Completion of the consent process can be deferred for up to 48 hours if (1) the parent/legal guardian is physically or emotionally unavailable and (2) the child is still in the acute phase of their illness. Implementing *RESTORE* during the acute phase of illness will not jeopardize the impact of the intervention. Patients can enter or transition to the Nurse-Implemented Goal-Directed Algorithm on Box 4 (if enrolled on intermittent sedation) or Box 12 (if enrolled on continuous infusions).

We will use a written layered consent process when inviting parents/legal guardians in the control and intervention groups to participate in the follow-up aspect of this study. Specifically, parents/legal guardians can agree to participate in the study with or without participation in the follow up aspect of the study.

All patients will be intubated, mechanically ventilated and sedated so will be unable to provide assent while acutely ill. Patients will be asked to provide assent when they are cognitively capable; specifically, when they are over 8 years of age, with a Pediatric Cerebral Performance Category of 1-3 (normal to moderate disability), 72 hours after their last sedative dose. Clinical sites will be instructed to follow their local IRB recommendations for the age of assent but, given the limitations of the study instruments, we will only survey children 8 years of age and older. (See Appendix I.D: Child Assent 8-12 years old; Appendix I.E: Child Assent 13-17 years old; Appendix I.F: Adolescent turning 18 years old after enrollment consent). Site coinvestigators will be asked to obtain the child's assent/consent for follow-up prior to hospital discharge. If this is not possible, the CRISMA team will ask the parent's/legal guardian's permission to assent their child or consent their 18 year old during their scheduled telephone appointment.

F.2.b Protection against risk

We will attempt to decrease the potential risks of the pediatric sedation management protocol by embedding the patient's pain and sedation assessments into clinical decision making and routinely assessing the patient's capacity for independent breathing and tolerance to sedation withdrawal. The *RESTORE* protocol includes coinvestigator walk rounds that serve to monitor patient safety and offer staff support and retraining as necessary. In addition, the *RESTORE* physician order templates will decrease delays in implementing a change in a patient's analgesia and sedation and include maximum dose ranges that require nurse-physician consultation.

Coding all subject data with a unique identification number will minimize risk to loss of subject confidentiality. Each Center's Log, linking Study ID Number to patient identity, will remain with the site coinvestigators in a locked file. None of the eCRFs will contain any personal identifying information, so that all information received by the DCC will have no identifiable patient data. At each site, all information that includes patient identifiers (e.g., copies of CRFs, etc.) will be placed in locked file cabinets. Risks associated with the study will be vigilantly monitored by the Principal Investigator, Steering Committee and Data and Safety Monitoring Board. Any publication arising from this study will maintain the anonymity of study participants.

The CRISMA center employs procedures to protect against the risk of unwanted loss or release of confidential information. Subject-specific hospital data and completed mailed and telephone questionnaire data will be made available only to Drs. Watson, Angus, Kong, and the CRISMA research staff. The only dataset with subject identifier information will be the subject tracking system used to follow-up and contact families. All other datasets will label subject records with a unique study number and be stripped of other identifying information; specifically, clinical data will not reside with identifying data. Questionnaire data will be kept in locked files and/or password-protected data files. All results will be described in aggregate without identification of individual subjects.

F.3 Potential Benefits of the Proposed Research to the Subjects and Others

Control and baseline patients will be receiving usual care. Potential benefits to the intervention subjects include shorter duration of mechanical ventilation, shorter time to recovery of acute respiratory failure, shorter time weaning from mechanical ventilation, expeditious assessment of neurological injury, less total exposure to comfort medications, shorter PICU and hospital lengths of stay, and less costly care. Potential benefits may outweigh potential risks.

We anticipate no direct benefits to most subjects and their families who participate in the follow-up study, although some may benefit from the contact provided during telephone interviews. If the CRISMA team determines a subject meets the criteria for PTSD, they will inform the study doctor so that appropriate referrals and/or follow-up can be made.

Society in general and future critically ill children and their families will benefit, however, from the study's results, which will provide a better understanding of how sedation can best be administered to critically ill children with acute respiratory failure.

F.4 Importance of the knowledge to be gained

This study addresses one of the most significant problems in all pediatric critical care. Mechanical ventilation typically represents an intervention that mandates on-going treatment in the PICU. It has been previously demonstrated that a frequent reason for inability to wean mechanical ventilation and proceed towards extubation is excessive sedation. In a focused effort to provide patient comfort, particularly during mechanical ventilation, clinicians practicing in PICUs may place children at unintentional, additional risk by virtue of prolonged need for mechanical ventilation, with the associated dangers of ventilator-associated lung injury, ventilator-associated pneumonia and blood stream infections.

In addition, there has been little effort to understand the long-term effects of high dose opiate and benzodiazapine administration, and their associated care costs. This study is unique in terms of testing an adequately explicit team approach for sedation/analgesia management which forces the care plan out of status quo, with an emphasis on weaning dosing of sedation and analgesics as soon as possible. This intervention is coupled with daily testing for extubation readiness.

Critical illness among children is a significant health problem in the US. Because of a generally long life expectancy, any impairment in a child can have consequences that last for decades. These consequences are extremely important for the individual. However, the consequences may also impact society at large in terms of cost to provide prolonged medical services and lost work productivity. For the first time a concerted effort will be made to examine the costs of implementing a formal sedation/analgesia protocol in addition to assessing potential long-term benefits and/or risks associated with sedation/analgesia during pediatric critical illness. This research has the real potential to significantly improve the way sedation/analgesia is practiced in PICUs. Knowledge gained trough this research will establish a standard of care that will influence clinician education, the care of the vast majority of pediatric patients supported on mechanical ventilation, and future studies evaluating new or different combinations of sedative agents.

F.5 Data and Safety Monitoring Plan

The Director, NHLBI, has appointed an independent Data and Safety Monitoring Board (DSMB). Members of the DSMB do not have any affiliation with the University of Pennsylvania or any collaborating institution. The DSMB will meet once prior to the start of the study and at least once during each study year, and more frequently as needed.

The DSMB is responsible for monitoring implementation of the protocol, oversight of subject safety and reviewing the quality of study data. The DSMB will approve the final protocol and any substantive changes to the protocol prior to implementation. The DSMB will review the progress of the trial, including assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome. The DSMB chair will receive reports of all serious adverse events throughout the conduct of the study. There will be three formal interim analyses after study outcomes have been obtained on approximately 400, 1200, and 1800 subjects, for the DSMB to assess whether or not to stop the study early for efficacy or futility. There will also be a review of study endpoints and adverse events by the Data and Safety Monitoring Board at these times, or as requested by the Data and Safety Monitoring Board. If the DSMB recommends a study change for patient safety or ethical reasons, or if the study is closed early due to slow accrual, the Principal Investigator will be responsible for implementing the recommendations as expeditiously as possible, according to standard NIH policies.

The DSMB may recommend that the trial be stopped if:

- The intervention is associated with an increased dependency on mechanical ventilation, increased mortality or increased adverse events.
- Compliance to the study protocol and/or recruitment is well below acceptable goals and the ability of the study to achieve its goals is seriously compromised.
- Evidence external to the study renders it unethical to continue the study.

F.6 Adverse Event Reporting

A description of all untoward or unfavorable occurrences during all phases of patient enrollment will be recorded on eCRFs. In addition, the required intervention(s), patient's condition after the event, an estimate of the extent of injury, and prevention strategies will be reported. The relationship of sedation management to the adverse event will be classified by the bedside clinicians as follows:

- Not related: The event is clearly related to factors such as the subject's clinical state, not with therapeutic interventions associated with sedation management.
- Possible: The event follows a reasonable temporal sequence from the titration of sedation and/or is consistent with known events related to the titration of sedation but is possibly related to factors such as the subject's clinical state.
- Probable: The event follows a reasonable temporal sequence from the titration of sedation and/or is consistent with known events related to the titration of sedation and cannot be reasonably explained by factors such as the subject's clinical state.
- Definitely: The event follows a reasonable temporal sequence from the titration of sedation and/or is consistent with known events related to the titration of sedation and cannot be reasonably explained by factors such as the subject's clinical state. In addition, the event occurs immediately following the titration of sedation, or improves on changing sedation, or reappears on repeat titration of sedation.

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

- Mild: Does not impact (in any way) 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, requires/prolongs inpatient hospitalization, persistent or significant disability/incapacity.

Site coinvestigators will report unanticipated, related or possibly related problems to their internal IRBs, the DCC and Dr. Curley within 24 hours. Dr Curley and local coinvestigators will immediately follow up on these problems and communicate with the DSMB and external IRBs per NIH guidelines. Site coinvestigators will report all SAEs to the DCC within 24 hours. All serious, unexpected adverse events that are possibly, probably or definitely related to the intervention will also be reported to Dr. Curley within 24 hours. Dr. Curley and local coinvestigators will immediately follow up on these SAEs and communicate with the DSMB and external IRBs per NIH guidelines. All adverse events will be reviewed monthly for trends. Non serious adverse events will be submitted to the DSMB twice yearly

F.7 Inclusion of Females and Minorities

Particular attention will be paid to gender and minority representation to ensure that the proportion of minority and female children enrolled in the study is similar to the population who are screened and found to meet eligibility criteria in each site. For comparison, we enrolled 47% females and 45% ethnic minorities in our pediatric prone study in patients with acute lung injury. (90) We do not expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. Given the lack of data to neither support nor negate significant differences in intervention effect between subgroups but we will conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups.

F.8 Inclusion of Children

All subjects will be children, >2 weeks of age (and 42 weeks corrected post menstrual age) to <18 years of age. This age group reflects the age group that is normally cared for in the PICU. The investigative team is specifically trained in the clinical management of critically ill infants, children, and adolescents. The clinical sites are all PICUs who normally admit patients within this age group.

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Appendix I: Consent Forms (Templates)

A. Baseline Phase

University of Pennsylvania

Research Subject
Informed Consent & HIPAA Authorization Form
Template – BASELINE PHASE

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Principal Investigator:
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Emergency Contact:

Why am I being asked to volunteer?

You are being invited to participate in a research study because your child requires pediatric intensive care for acute respiratory distress (breathing problem) and requires a ventilator (breathing machine). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you or your child are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you/your child will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the research team about this form. If you decide to allow your child to participate, you will be asked to sign this form.

What is the purpose of this research study?

This study is being done because we are trying to learn the best way to keep children comfortable and safe when they are on a ventilator, while at the same time limiting short-term and long-term risks. The purpose of this study is to evaluate whether a standardized, protocol-driven approach to managing the way sedative (calming) medications are used in children is better than the usual approach. Specifically, we will determine if the proposed approach effects

(1) how long children need to be on a ventilator, (2) the cost of sedation management and (3) the quality of a child's life and emotional health after hospital discharge.

Children who require intensive care and a ventilator also receive sedative medication to keep them comfortable and safe. In contrast to these benefits, we know that the more sedation is used, the longer it takes for a child to get off the ventilator which increases their risk for complications (for example, developing pneumonia on the ventilator).

Recent studies in adult intensive care have shown that when doctors and nurses work together as a team and use a guideline to manage sedation, patients come off the ventilator faster with fewer side effects. This strategy includes doctor and nurse training and agreement on which sedatives are used when patients are on ventilators, having doctors and nurses jointly identify a daily sedation goal for a patient, having nurses use a plan to guide changes in a patient's sedatives based on that goal, and keeping track of patient care so that doctors and nurses can evaluate how well they manage a patient's sedation. The information we have on this strategy shows that most adult patients have good control of their pain and anxiety and that they have no memory of waking up from sedation after they are sent home from the hospital.

We have preliminary information that shows that a pediatric sedation management guideline may also be helpful in caring for children on ventilators. Currently it is impossible to know for certain the best way to keep children comfortable and safe while on a breathing machine unless we compare one group of children whose sedation is managed in the usual way to one group of children whose sedation is managed with the proposed pediatric sedation management guideline.

Approximately 26 pediatric intensive care units are working together to evaluate a pediatric sedation management guideline in children who need to be on ventilators to support their breathing and following up on these children after hospital discharge.

About half of the intensive care units will be randomly selected (by chance) to train doctors and nurses to use the pediatric sedation management guideline.

About half of the intensive care units will be randomly selected (by chance) to continue what they normally do and not change the way doctors and nurses manage sedation.

The aim of this study is to conduct a multicenter clinical trial to test whether pediatric patients with acute respiratory distress managed with the pediatric sedation management guideline experience better outcomes than patients receiving usual care.

How long will I be in the study? How many other people will be in the study?

You are being asked to allow your child to participate in this study from the time their breathing tube is inserted until 72 hours after receiving their last sedative medication, until hospital discharge, or for a maximum of 28 days. If your child is still in the hospital after 28 days, then we will also review your child's medical records at hospital discharge or up to 90 days. The purpose of this chart review is to check for late occurring problems; for example, infection.

We plan to enroll almost 2,900 children (between 2 weeks and 18 years of age) in approximately 26 different pediatric intensive care units. We expect to enroll approximately ____ children from this intensive care unit.

What am I being asked to do?

We are currently in the 3 month Baseline Data Collection phase of this study. During this time all participating pediatric intensive care units are collecting the same information so that we can describe the usual way doctors and nurses in this intensive care unit manage a child's sedation while on a ventilator. We have not changed our usual way of managing sedation.

You are being asked to allow us to collect information from your child's medical record every day (including your child's age, medical problem, comfort levels, sedative use, treatments given and how long your child is in the hospital).

What are the possible risks or discomforts?

Any time confidential information is collected, there is a risk that information will be unintentionally released. Any information about you or your child obtained from this research will be kept as confidential (private) as possible.

All paper records related to your/your child's involvement in this research study will be stored in locked file cabinets. Computerized records are password protected. Your/your child's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers with your/your child's identity will be kept separate from the research records.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you and/or your child. This includes information that, once learned, might cause you to change your mind about your child being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You and your child are not expected to get any benefit from being in this research study. Future children who receive sedation in the ICU and their families may benefit from this study, which will provide a better understanding of how best to use sedatives in children on ventilators.

What other choices do I have if I do not participate?

If you choose not to participate, your child's information will not be collected. How we manage your child's sedation will not change if you decide to take part in this study or not.

Will I be paid for being in this study?

Neither you nor your child will be paid for being in this study.

Will I have to pay for anything?

There will be no cost to you for your child to be in this research study. Care that would be given if your child was not in this research study will be charged under your usual payment method. There will be no charge to you or your insurance company for any of the costs directly related to this study.

What happens if I am injured or hurt during the study?

Because this study involves examining your child's medical record, it is extremely unlikely that you or your child could be injured or become ill as a result of participating in this study. You do not, however, waive any legal rights by signing this form. In the event that you or your child are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

When is the study over? Can I leave the study before it ends?

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your or your child's future care.

This study is expected to end after all information has been collected and reviewed. This study may also be stopped at any time by your child's doctor, the study Principal Investigator and the study Sponsor (National Institutes of Health) without your consent because it is necessary for your or your child's health or safety. Such an action would not require your or your child's consent, but you will be informed if such a decision is made and the reason for this decision.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information in your child's medical record will be kept private. However, we cannot guarantee total privacy. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your/your child's name and other personal information will not be used. The information we obtain for the study will be sent to the University of Pennsylvania School of Nursing (Lead Center), the Children's Hospital, Boston (Data Coordination Center), and the National Institutes of Health (Sponsor). They will be examining the research records for quality assurance and data analysis.

All information sent to the University of Pennsylvania School of Nursing and the Data Coordination Center at Children's Hospital, Boston will not have any of your/your child's identifying information on it.

What information about my child may be collected, used or shared with others?

This part of the form gives more detailed information about how your/your child's personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

- Name, address, telephone number, date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is my child's information being used?

Your child's information is used by the research team to contact you/your child during the study. Your child's information and results of tests and procedures are used to:

- do the research
- oversee the research

- to see if the research was done right.

Who may use and share information about my child?
The following individuals may use or share your child's information for this research study:

- The investigator for the study and the study team
- Authorized personnel at **[NAME OF CENTER]**

Who, outside of the [NAME OF CENTER], might receive my child's information?

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor

Oversight organizations

- The Office of Human Research Protections
- The study data and safety monitoring board

Once your child's personal health information is disclosed to others outside the **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your child's active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your/your child's privacy.

How long may the [NAME OF CENTER] use or disclose my child's personal health information?
Your authorization for use of your child's personal health information for this specific study does not expire.

Your child's information may be held in a research database. However, the **[NAME OF CENTER]** may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The **[NAME OF CENTER]** Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my child's information?
Yes. You may withdraw or take away your permission to use and disclose your child's health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, your child will not be able to stay in this study.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your child's participation in this research study or if you have any questions about your child's rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Nursing to use your child's personal health information collected for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Nursing to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent and HIPAA authorization form will be given to you. You will also be given the University of Pennsylvania Health System and School of Nursing's Notice of Privacy Practices that contains more information about the privacy of your/your child's health information.

Consent

_____
Name of Subject (Please Print)

_____	_____	_____
Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date
_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date

B. Control/Usual Care

University of Pennsylvania
RESEARCH SUBJECT
INFORMED CONSENT & HIPAA AUTHORIZATION FORM
Template – Control/Usual Care

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

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Emergency Contact:

Why am I being asked to volunteer?
You are being invited to participate in a research study because your child requires pediatric intensive care for acute respiratory distress (breathing problem) and requires a ventilator (breathing machine). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you or your child are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you/your child will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the research team about this form. If you decide to allow your child to participate, you will be asked to sign this form.

What is the purpose of this research study?
This study is being done because we are trying to learn the best way to keep children comfortable and safe when they are on a ventilator, while at the same time limiting short-term and long-term risks. The purpose of this study is to evaluate whether a standardized, protocol-driven approach to managing the way sedative (calming) medications are used in children is better than the usual approach. Specifically, we will determine if the proposed approach effects (1) how long children need to be on a ventilator, (2) the cost of sedation management and (3) the quality of a child's life and emotional health after hospital discharge.

Children who require intensive care and a ventilator also receive sedative medication to keep them comfortable and safe. In contrast to these benefits, we know that the more sedation is used, the longer it takes for a child to get off the ventilator which increases their risk for complications (for example, developing pneumonia on the ventilator).

Recent studies in adult intensive care have shown that when doctors and nurses work together as a team and use a guideline to manage sedation, patients come off the ventilator faster with fewer side effects. This strategy includes doctor and nurse training and agreement on which sedatives are used when patients are on ventilators, having doctors and nurses jointly identify a daily sedation goal for a patient, having nurses use a plan to guide changes in a patient's sedatives based on that goal, and keeping track of patient care so that doctors and nurses can evaluate how well they manage a patient's sedation. The information we have on this strategy shows that most adult patients have good control of their pain and anxiety and that they have no memory of waking up from sedation after they are sent home from the hospital.

We have preliminary information that shows that a pediatric sedation management guideline may also be helpful in caring for children on ventilators. Currently it is impossible to know for certain the best way to keep children comfortable and safe while on a breathing machine unless we compare one group of children whose sedation is managed in the usual way to one group of children whose sedation is managed with the proposed pediatric sedation management guideline.

Approximately 26 pediatric intensive care units are working together to evaluate a pediatric sedation management guideline in children who need to be on ventilators to support their breathing and following up on these children after hospital discharge.

About half of the intensive care units will be randomly selected (by chance) to train doctors and nurses to use the pediatric sedation management guideline.

About half of the intensive care units will be randomly selected (by chance) to continue what they normally do and not change the way doctors and nurses manage sedation.

The aim of this study is to conduct a multicenter clinical trial to test whether pediatric patients with acute respiratory distress managed with the pediatric sedation management guideline experience better outcomes than patients receiving usual care.

How long will I be in the study? How many other people will be in the study?

You are being asked to allow your child to participate in this study from the time their breathing tube is inserted until 72 hours after receiving their last sedative medication, until hospital discharge, or for a maximum of 28 days. If your child is still in the hospital after 28 days then we will also review your child's medical records at hospital discharge or up to 90 days. The purpose of this chart review is to check for late occurring problems; for example, infection.

You are also being asked to allow our research team to contact you once 6 months after discharge from the pediatric intensive care unit (PICU). For this part of the study, we will randomly (by chance) invite about half of the families to take part in a mailed or web-based survey and telephone-based interview conducted by the CRISMA center (Clinical Research, Investigation, and Systems Modeling of Acute Illness center) at the University of Pittsburgh.

We plan to enroll almost 2,900 children (between 2 weeks and 18 years of age) in approximately 26 different pediatric intensive care units. We expect to enroll approximately ____ children from this intensive care unit.

What am I being asked to do?

Our pediatric intensive care unit was randomly selected (by chance) to manage sedation in children on a breathing machine (ventilator) for acute respiratory distress using our usual care. That means we will not change the way we will manage your child's sedation while on a ventilator.

If you agree to participate we will collect information from your child's medical record every day (including your child's age, medical problem, comfort levels, sedative use, treatments given, and how long your child is in the hospital). The information we collect will help us describe the usual way a pediatric intensive care team manages a child's sedation while on a ventilator.

In addition, we will send a copy of this consent form and some information about you and your child to our research team at the CRIMSA research center at the University of Pittsburgh for the follow up part of the study. If selected, personnel from the CRIMSA research team will contact you six months after your child is discharged from the pediatric intensive care unit (PICU) for a follow-up survey and telephone interview. At that time, they will send you some surveys to complete by mail or, if you prefer, via the internet. Several weeks later, they will make a telephone appointment to speak with you. They will ask you questions about how your child is feeling, how he/she is doing medically, and whether he/she has received any additional medical care. The interview will take 7 to 20 minutes to complete, depending on your child's age.

(Children's Hospital & Research Center at Oakland, Dartmouth-Hitchcock Medical Center, Monroe Carell, Jr Children's Hospital at Vanderbilt, and St. Louis Children's Hospital) If your child is also participating in the NIH-sponsored Critical Pertussis study, the results from the 6 month follow-up survey and telephone interview (described above) will be shared with the Critical Pertussis Collaborative Pediatric Critical Care Research Network. Both studies are collecting the same information at 6 months after PICU discharge. By sharing the information, you will only need to answer the survey questions once.

If you choose not to participate, we will not collect information on your child or contact you for a follow-up interview. You can agree to participate in this study with or without the follow-up part of the study.

What are the possible risks or discomforts?

Any time confidential information is collected, there is a risk that information will be unintentionally released. Any information about you or your child obtained from this research will be kept as confidential (private) as possible.

All paper records related to your/your child's involvement in this research study will be stored in locked file cabinets. Computerized records are password protected. Your/your child's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers with your/your child's identity will be kept separate from the research records.

If you and your child are selected to participate in the follow-up part of the study, there is a risk of possible discomfort in answering questions on the survey. To minimize this risk, you will be

provided a copy of the survey beforehand, and you always have an option to skip questions or end the conversation at any time.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you and/or your child. This includes information that, once learned, might cause you to change your mind about your child being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You and your child are not expected to get any benefit from being in this research study.

If the CRISMA team determines that your child meets the criteria for Post-Traumatic-Stress Disorder (PTSD), they will inform the study doctor so that appropriate referrals and/or follow-up can be made.

Future children who receive sedation in the intensive care unit and their families may benefit from this study, which will provide a better understanding of how best to use sedatives in children on ventilators.

What other choices do I have if I do not participate?

If you choose not to participate, your child's information will not be collected and you will not be contacted for a follow-up part of this study. How we manage your child's sedation will not change if you decide to take part in this study or not.

Will I be paid for being in this study?

Neither you nor your child will be paid for being in this study.

Will I have to pay for anything?

There will be no cost to you for your child to be in this research study. Care that would be given if your child was not in this research study will be charged under your usual payment method. There will be no charge to you or your insurance company for any of the costs directly related to this study.

What happens if I am injured or hurt during the study?

Because this study involves examining your child's medical record, filling out surveys and talking on the telephone it is extremely unlikely that you or your child could be injured or become ill as a result of participating in this study. You do not, however, waive any legal rights by signing this form. In the event that you or your child are hurt or injured as a result of participation in this research study, please contact the investigator listed on page one of this form.

When is the Study over? Can I leave the Study before it ends?

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your or your child's future care.

This study is expected to end after all information has been collected and reviewed. This study may also be stopped at any time by your child's doctor, the study Principal Investigator and the study Sponsor (National Institutes of Health) without your consent because it is necessary for your or your child's health or safety. Such an action would not require your or your child's consent, but you will be informed if such a decision is made and the reason for this decision. You may also be removed from the research study by the Principal Investigator if, for example, the CRISMA researchers cannot get in touch with you to conduct the follow-up part of study.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information in your child's medical record will be kept private. However, we cannot guarantee total privacy. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your/your child's name and other personal information will not be used. The information we obtain for the study will be sent to the University of Pennsylvania School of Nursing (Lead Center), the Children's Hospital, Boston (Data Coordination Center), CRISMA Center at the University of Pittsburgh (Coordinating patient Follow up), and the National Institutes of Health (Sponsor). They will be examining the research records for quality assurance and data analysis.

All information sent to the University of Pennsylvania School of Nursing and the Data Coordination Center at Children's Hospital, Boston will not have any of your/your child's identifying information on it.

If you agree to participate in the follow up part of this study, a copy of this signed consent form along with demographic and contact information will be sent directly to the CRISMA Center at the University of Pittsburgh. Information will be sent via secure FAX or encrypted e-mail. All data will be secured for the purpose of confidentiality, and data will be used only for research purposes. The only dataset with subject identifier information will be the subject tracking system used to follow-up and contact families. All other datasets will label subject records with a unique study number and be stripped of other identifying information.

What information about my child may be collected, used or shared with others?

This part of the form gives more detailed information about how your/your child's personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

- Name, address, telephone number, date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is my child's information being used?

Your child's information is used by the research team to contact you/your child during the study. Your child's information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right.

Who may use and share information about my child?
The following individuals may use or share your child's information for this research study:

- The investigator for the study and the study team
- Authorized personnel at **[NAME OF CENTER]**

Who, outside of the [NAME OF CENTER], might receive my child's information?

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness Center) at the University of Pittsburgh (the follow-up coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor

Oversight organizations

- The Office of Human Research Protections
- The study data and safety monitoring board

Once your child's personal health information is disclosed to others outside the **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your child's active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your/your child's privacy.

How long may the [NAME OF CENTER] use or disclose my child's personal health information?
Your authorization for use of your child's personal health information for this specific study does not expire.

Your child's information may be held in a research database. However, the **[NAME OF CENTER]** may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The **[NAME OF CENTER]** Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my child's information?
Yes. You may withdraw or take away your permission to use and disclose your child's health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, your child will not be able to stay in this study.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your child's participation in this research study or if you have any questions about your child's rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Nursing to use your child's personal health information collected for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Nursing to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this informed consent and HIPAA authorization form will be given to you. You will also be given the University of Pennsylvania Health System and School of Nursing's Notice of Privacy Practices that contains more information about the privacy of your/your child's health information.

Consent

_____
Name of Subject (Please Print)

_____	_____	_____
Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date

_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date

Consent for follow-up part of the study

If your child is selected for the follow-up study, do you agree to allow research personnel from CRISMA to contact you and/or your child?

_____ Yes _____ No

_____	_____ _____
Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian Date

_____	_____ _____
Name of Person Obtaining Consent (Please Print)	Signature Date

Child Assent for follow-up part of the study (over 8 years)

VERIFICATION OF EXPLANATION / ASSENT:

I certify that I have carefully explained the purpose and nature of this research study to the above named child in age appropriate language.

Specifically, I've explained that he/she is being asked questions because he/she was in the hospital about 6 months ago.

I've explained that he/she will be asked questions about their health and activities, about their feelings, about how they get along with others, and about their school activities.

I've explained that he/she will be also asked their opinion on how bothered they have been in the past 2 weeks on problems some kids have had after being in the hospital.

He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

_____ _____

Investigator's Signature Date

C. Intervention/Guideline

University of Pennsylvania
RESEARCH SUBJECT
INFORMED CONSENT & HIPAA AUTHORIZATION FORM
Template – Intervention/Guideline

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Principal Investigator:
Martha A.Q. Curley, RN, PhD, FAAN
Associate Professor; Standing Faculty
University of Pennsylvania
School of Nursing
Claire M. Fagin Hall
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Emergency Contact:

Why am I being asked to volunteer?
You are being invited to participate in a research study because your child requires pediatric intensive care for acute respiratory distress (breathing problem) and requires a ventilator (breathing machine). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you or your child are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you/your child will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the research team about this form. If you decide to allow your child to participate, you will be asked to sign this form.

What is the purpose of this research study?
This study is being done because we are trying to learn the best way to keep children comfortable and safe when they are on a ventilator, while at the same time limiting short-term and long-term risks. The purpose of this study is to evaluate whether a standardized, protocol-driven approach to managing the way sedative (calming) medications are used in children is better than the usual approach. Specifically, we will determine if the proposed approach effects (1) how long children need to be on a ventilator, (2) the cost of sedation management and (3) the quality of a child's life and emotional health after hospital discharge.

Children who require intensive care and a ventilator also receive sedative medication to keep them comfortable and safe. In contrast to these benefits, we know that the more sedation is used, the longer it takes for a child to get off the ventilator which increases their risk for complications (for example, developing pneumonia on the ventilator).

Recent studies in adult intensive care have shown that when doctors and nurses work together as a team and use a guideline to manage sedation, patients come off the ventilator faster with fewer side effects. This strategy includes doctor and nurse training and agreement on which sedatives are used when patients are on ventilators, having doctors and nurses jointly identify a daily sedation goal for a patient, having nurses use a plan to guide changes in a patient's sedatives based on that goal, and keeping track of patient care so that doctors and nurses can evaluate how well they manage a patient's sedation. The information we have on this strategy shows that most adult patients have good control of their pain and anxiety and that they have no memory of waking up from sedation after they are sent home from the hospital.

We have preliminary information that shows that a pediatric sedation management guideline may also be helpful in caring for children on ventilators. Currently it is impossible to know for certain the best way to keep children comfortable and safe while on a breathing machine unless we compare one group of children whose sedation is managed in the usual way to one group of children whose sedation is managed with the proposed pediatric sedation management guideline.

Approximately 26 pediatric intensive care units are working together to evaluate a pediatric sedation management guideline in children who need to be on ventilators to support their breathing and following up on these children after hospital discharge.

About half of the intensive care units will be randomly selected (by chance) to train doctors and nurses to use the pediatric sedation management guideline.

About half of the intensive care units will be randomly selected (by chance) to continue what they normally do and not change the way doctors and nurses manage sedation.

The aim of this study is to conduct a multicenter clinical trial to test whether pediatric patients with acute respiratory distress managed with the pediatric sedation management guideline experience better outcomes than patients receiving usual care.

How long will I be in the study? How many other people will be in the study?

You are being asked to allow your child to participate in this study from the time their breathing tube is inserted until 72 hours after receiving their last sedative medication, until hospital discharge, or for a maximum of 28 days

If your child is still in the hospital after 28 days then we will also review your child's medical records at hospital discharge or up to 90 days. The purpose of this chart review is to check for late occurring problems; for example, infection.

You are also being asked to allow our research team to contact you once 6 months after discharge from the pediatric intensive care unit (PICU). For this part of the study, we will randomly (by chance) invite about half of the families to take part in a mailed or web-based survey and telephone-based interview conducted by the CRISMA center (Clinical Research, Investigation, and Systems Modeling of Acute Illness center) at the University of Pittsburgh.

We plan to enroll almost 2,900 children (between 2 weeks and 18 years of age) in approximately 26 different pediatric intensive care units. We expect to enroll approximately ____ children from this intensive care unit.

What am I being asked to do?

Our pediatric intensive care unit was randomly selected (by chance) to manage sedation in children on a breathing machine (ventilator) for acute respiratory distress using the pediatric sedation management guideline. You are being asked to decide whether your child's clinical team can use this guideline to help manage your child's sedation.

This pediatric sedation management guideline includes:

- having your child's doctor and nurse agree on which sedatives to use when your child is on the ventilator;
- having your child's doctor and nurses discuss how your child is doing and jointly identify a daily sedation goal for your child;
- having your child's nurses use a decision tool to guide moment-to-moment changes in your child's sedatives based on that daily goal; and
- keeping track of your child's sedation so that your child's clinical team can receive feedback on your child's sedation management.

The daily sedation goal and the medications used to achieve these goals are prescribed by your child's doctor and implemented by your child's nurse each day. The decision tool provides a consistent way of managing your child's sedation that matches your child's illness and recovery. For example, when your child is in the acute phase of their illness, the decision tool suggests a way to keep your child well sedated. When your child starts to get better, the decision tool suggests a way to help the clinical team use the lowest effective dose of sedation and evaluates your child's ability to come off the ventilator each day. Once your child no longer needs the ventilator to breathe, the decision tool suggests a way to help your child's clinical team discontinue your child's sedatives.

Our usual care does not routinely include all four aspects of this pediatric sedation guideline including the pediatric decision tool.

If you agree to participate, we will use the pediatric sedation management guideline to direct your child's sedation and we will collect information from your child's medical record every day. This information will include your child's age, medical problem, comfort levels, sedative use, treatments given, and how long your child is in the hospital.

In addition, we will send a copy of this consent form and some information about you and your child to our research team at the CRIMSA research center at the University of Pittsburgh for the follow up part of the study. If selected, personnel from the CRIMSA research team will contact you six months after your child is discharged from the pediatric intensive care unit (PICU) for a follow-up survey and telephone interview. At that time, they will send you some surveys to complete by mail or, if you prefer, via the internet. Several weeks later, they will make a telephone appointment to speak with you. They will ask you questions about how your child is feeling, how he/she is doing medically, and whether he/she has received any additional medical care. The interview will take 7 to 20 minutes to complete, depending on your child's age.

(Children's Hospital & Research Center at Oakland, Dartmouth-Hitchcock Medical Center, Monroe Carell, Jr Children's Hospital at Vanderbilt, and St. Louis Children's Hospital) If your

child is also participating in the NIH-sponsored Critical Pertussis study, the results from the 6 month follow-up survey and telephone interview (described above) will be shared with the Critical Pertussis Collaborative Pediatric Critical Care Research Network. Both studies are collecting the same information at 6 months after PICU discharge. By sharing the information, you will only need to answer the survey questions once.

If you choose not to participate, we will not use the sedation management guideline, we will not collect information from your child's medical record and we will not contact you for the follow-up part of this study. You can agree to participate in this study with or without the 6 month follow-up part of the study.

What are the possible risks or discomforts?

Potential short-term risks or discomforts linked to the use of sedation in both children and adults on ventilators include:

- inadequate pain management
- inadequate sedation management – over sedation or agitation
- iatrogenic withdrawal symptoms from weaning sedation too fast
- unplanned removal of the breathing tube
- airway irritation from movement of the breathing tube
- reinsertion of the breathing tube within 24 hours
- dislodgement of vascular access or drainage tubes
- pneumonia from the ventilator
- infection from the use of intravenous catheters and
- pressure ulcers on weight-bearing surfaces from not moving

We will try to decrease these potential risks by assessing your child's pain, sedation level, and tolerance to sedation withdrawal. We will also assess your child's capacity to breathe without the ventilator every day. We will try to respond quickly to these assessments by adjusting your child's medication as appropriate.

Potential long-term risks linked to the use of sedation in adults on ventilators include Post Traumatic Stress Disorder (PTSD). We do not have any similar information in children.

Any time confidential information is collected, there is a risk that information will be unintentionally released. Any information about you or your child obtained from this research will be kept as confidential (private) as possible.

All paper records related to your/your child's involvement in this research study will be stored in locked file cabinets. Computerized records are password protected. Your/your child's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers with your/your child's identity will be kept separate from the research records.

If you and your child are selected to participate in the follow-up part of the study, there is a risk of possible discomfort in answering questions on the survey. To minimize this risk, you will be provided a copy of the survey beforehand, and you always have an option to skip questions or end the conversation at any time.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you and/or your child. This includes information that, once learned, might cause you to change your mind about your child being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

We cannot and do not guarantee or promise that you or your child will receive any benefits from this study. Possible benefits of study participation include shorter time on the ventilator, shorter time for the recovery of acute respiratory distress, earlier detection of neurological problems, decreased sedative exposure and problems linked to sedation, and decreased intensive care and hospital stay.

If the CRISMA team determines a child meets the criteria for Post-Traumatic-Stress Disorder (PTSD), they will inform the study doctor so that appropriate referrals and/or follow-up can be made.

Future children who receive sedation in the intensive care unit and their families may benefit from this study, which will provide a better understanding of how best to use sedatives in children on ventilators.

What other choices do I have if I do not participate?

If you choose not to participate, your child's care team will still do what they think is best for your child, but they will not follow the pediatric sedation management guideline. Your child's information will not be collected and you will not be contacted for a follow-up interview.

Will I be paid for being in this study?

Neither you nor your child will be paid for being in this study.

Will I have to pay for anything?

There will be no cost to you for your child to be in this research study. Care that would be given if your child was not in this research study will be charged under your usual payment method. There will be no charge to you or your insurance company for any of the costs directly related to this study.

What happens if I am injured or hurt during the study?

All forms of medical diagnosis and treatment involve some risk of injury. In spite of all precautions, you or your child might develop an injury from participating in this study. If such injuries arise, we will help you get reasonable, immediate, and necessary medical care for your and/or your child's injury. Reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, our research staff will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

Additionally, we are not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

When is the Study over? Can I leave the Study before it ends?

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your or your child's future care.

This study is expected to end after all information has been collected and reviewed. This study may also be stopped at any time by your child's doctor, the study Principal Investigator and the study Sponsor (National Institutes of Health) without your consent because it is necessary for your or your child's health or safety. Such an action would not require your or your child's consent, but you will be informed if such a decision is made and the reason for this decision. You may also be removed from the research study by the Principal Investigator if, for example, the CRISMA researchers cannot get in touch with you to conduct the follow-up part of study.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information in your child's medical record will be kept private. However, we cannot guarantee total privacy. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your/your child's name and other personal information will not be used. The information we obtain for the study will be sent to the University of Pennsylvania School of Nursing (Lead Center), the Children's Hospital, Boston (Data Coordination Center), CRISMA Center at the University of Pittsburgh (Coordinating patient Follow up), and the National Institutes of Health (Sponsor). They will be examining the research records for quality assurance and data analysis.

All information sent to the University of Pennsylvania School of Nursing and the Data Coordination Center at Children's Hospital, Boston will not have any of your/your child's identifying information on it.

If you agree to participate in the follow up part of this study, a copy of this signed consent form along with demographic and contact information will be sent directly to the CRISMA Center at the University of Pittsburgh. Information will be sent via secure FAX or encrypted e-mail. All data will be secured for the purpose of confidentiality, and data will be used only for research purposes. The only dataset with subject identifier information will be the subject tracking system used to follow-up and contact families. All other datasets will label subject records with a unique study number and be stripped of other identifying information.

What information about my child may be collected, used or shared with others?
This part of the form gives more detailed information about how your/your child's personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

- Name, address, telephone number, date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is my child's information being used?
Your child's information is used by the research team to contact you/your child during the study. Your child's information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right.

Who may use and share information about my child?
The following individuals may use or share your child's information for this research study:

- The investigator for the study and the study team
- Authorized personnel at **[NAME OF CENTER]**

Who, outside of the [NAME OF CENTER], might receive my child's information?

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness Center) at the University of Pittsburgh (the follow-up coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor

Oversight organizations

- The Office of Human Research Protections
- The study data and safety monitoring board

Once your child's personal health information is disclosed to others outside the **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your child's active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your/your child's privacy.

How long may the [NAME OF CENTER] use or disclose my child's personal health information?
Your authorization for use of your child's personal health information for this specific study does not expire.

Your child's information may be held in a research database. However, the **[NAME OF CENTER]** may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The **[NAME OF CENTER]** Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my child's information?
Yes. You may withdraw or take away your permission to use and disclose your child's health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, your child will not be able to stay in this study.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your child's participation in this research study or if you have any questions about your child's rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Nursing to use your child's personal health information collected for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Nursing to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this informed consent and HIPAA authorization form will be given to you. You will also be given the University of Pennsylvania Health System and School of Nursing's Notice of Privacy Practices that contains more information about the privacy of your/your child's health information.

Consent

_____
Name of Subject (Please Print)

_____	_____	_____
Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date

_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date

Consent for follow-up part of the study

If your child is selected for the follow-up study, do you agree to allow research personnel from CRISMA to contact you and/or your child?

_____ Yes _____ No

_____	_____	_____
Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date

_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date

Child assent for follow-up part of the study (over 8 years)

VERIFICATION OF EXPLANATION / ASSENT:

I certify that I have carefully explained the purpose and nature of this research study to the above named child in age appropriate language.

Specifically, I've explained that he/she is being asked questions because he/she was in the hospital about 6 months ago.

I've explained that he/she will be asked questions about their health and activities, about their feelings, about how they get along with others, and about their school activities.

I've explained that he/she will be also asked their opinion on how bothered they have been in the past 2 weeks on problems some kids have had after being in the hospital.

He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

_____ _____

Investigator's Signature Date

D. Assent for follow up: Child 8-12 years

University of Pennsylvania
RESEARCH Subject Assent Form
Template – Child 8-12 years

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Principal Investigator: Martha A.Q. Curley, RN, PhD, FAAN
Associate Professor; Standing Faculty
University of Pennsylvania
School of Nursing
Claire M. Fagin Hall
418 Curie Boulevard, Room 424
Philadelphia, PA 19104-4217 USA
Office Phone: 215.573.9449
Email: curley@nursing.upenn.edu

Emergency Contact:

Why are we meeting with you?

We want to tell you about something we are doing called a research study. A research study is when people collect a lot of information to learn more about something. Some of the people who work here are doing a study to learn more about children who needed to be on a machine to help them breathe when they were in the hospital. After we tell you about it, we will ask if you'd like to be in this study or not.

Why are we doing this study?

While you were sick in the intensive care unit you were on a machine to help you breathe. You also received medicines to help you feel calm and safe. We don't know a lot about what happens to children after they get better from this time.

We are working with about 25 other hospitals to see how children who were in the intensive care unit are doing after going home from the hospital. We want to find out if the medicines that helped them feel calm on the breathing machine affects how they feel after going home from the hospital.

What will you be asked to do and how long will it take?

Only if you agree, here's what will happen:

1. A copy of this form and some of your personal information will be sent to people at the University of Pittsburgh (in Pennsylvania).

2. They will pick one-half of the people who agree to be in the study. If you are picked, they will send you two surveys in the mail that ask you some questions about how you feel. You can either fill them out and mail them back or complete them on the internet. This would happen once and take about 10 minutes for you to answer the questions. They will also call on the telephone to talk with your parents about how things are going and to see if you have any questions about the surveys.

Will this study hurt?

No. Some of the questions might make you uncomfortable. If that happens, you don't have to answer the question or you can decide not to answer any of the questions.

Will you get better if you are in this study?

No, this study won't make you get well. You might feel better talking to somebody about how you feel. We hope we'll find out something that will help other children like you later.

Do you have any questions?

You can ask questions any time. You can ask now. You can ask later. You can talk to me or you can talk to someone else.

Do you have to be in this study?

No, you don't. No one will be mad at you if you don't want to do this. If you don't want to be in this study, just tell us. Or if you do want to be in the study, tell us that. And, remember, you can say yes now and change your mind later. It's up to you. We will give you a copy of this form to keep.

****

SIGNATURE OF PERSON CONDUCTING ASSENT DISCUSSION

I have explained the study to _____(print name of child here) in language he/she can understand, and the child has agreed to be in the study.

_____
Signature of Person Conducting Assent Discussion

_____ _____
Name of Person Conducting Assent Discussion (print) Date

_____ _____ _____
Signature of Child Participant Printed Name of Child Participant Date

E. Assent for follow up: Child 13-17 years

University of Pennsylvania
RESEARCH Subject Assent Form
Template – Child 13-17 years

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Principal Investigator: Martha A.Q. Curley, RN, PhD, FAAN
Associate Professor; Standing Faculty
University of Pennsylvania
School of Nursing
Claire M. Fagin Hall, Room 424
418 Curie Boulevard
Philadelphia, PA 19104-4217 USA
Office Phone: 215.573.9449
Email: curley@nursing.upenn.edu

Emergency Contact:

Why are we meeting with you?

You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study.

Why are we doing this study?

While you were sick in the intensive care unit you were on a breathing machine and you received medicines to help keep you comfortable and safe. We don't know a lot about teens who are recovering from this time in their lives. We are working with about 25 other hospitals to see how teens like you are doing after going home from the hospital.

The purpose of this study is to see if the way medicines are being used in teenagers on breathing machines affects how they feel after hospital discharge.

What will you be asked to do and how long will it take?

If you agree to join this study you may be sent two surveys in the mail that ask you some questions about how you feel. You can either fill them out and mail them back or complete them on the internet. This would happen once and take about 10 minutes for you to answer the questions. They will also call on the telephone to talk with your parents about how things are going and to see if you have any questions about the surveys.

Will this study hurt?

Some people don't like answering questions about themselves but you do not have to answer any questions that you don't want to. The questions take about 10 minutes.

Will you get better if you are in this study?

We do not know if being in this study will help you, but you might feel better thinking about how you feel. We may learn something that will help other children who spend time in the hospital.

Do you have to be in this research study and can you stop if you want to?

You can talk this over with your [mom/dad/guardian] before you decide. You do not have to join this study. It is up to you. You can say okay now and change your mind later. No one will be mad at you if you don't want to be in the study or if you join the study and later change your mind.

Do you have any questions?

We will answer any questions you have before you say yes or no to being in this study. If you have any questions about the study, please feel free to contact _____. If you sign your name below, it means that you agree to take part in this research study.

SIGNATURE OF PERSON CONDUCTING ASSENT DISCUSSION

I have explained the study to _____(*print name of Adolescent here*) in language he/she can understand, and the adolescent has agreed to be in the study.

_____
Signature of Person Conducting Assent Discussion

_____ _____
Name of Person Conducting Assent Discussion (*print*) Date

_____ _____ _____
Signature of Adolescent Participant Printed Name of Adolescent Date

F. Consent for follow up: 18 years

University of Pennsylvania

RESEARCH SUBJECT
INFORMED CONSENT & HIPAA AUTHORIZATION FORM
Template – Adolescent turning 18 years old after Enrollment

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure

Principal Investigator:
Martha A.Q. Curley, RN, PhD, FAAN
Associate Professor; Standing Faculty
University of Pennsylvania
School of Nursing
Claire M. Fagin Hall
418 Curie Boulevard, Room 424
Philadelphia, PA 19104-4217 USA
Office Phone: 215.573.9449
Email: curley@nursing.upenn.edu

Emergency Contact:

Why am I being asked to volunteer?

You are being invited to participate in a research study because you required pediatric intensive care for acute respiratory distress (breathing problem) and you required a ventilator (breathing machine). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

This study is being done because we are trying to learn the best way to keep children comfortable and safe when they are on a ventilator, while at the same time limiting short-term and long-term risks. The purpose of this study is to evaluate whether a standardized, protocol-driven approach to managing the way sedative (calming) medications are used in children is better than the usual approach. Specifically, we will determine if the proposed approach effects

(1) how long children need to be on a ventilator, (2) the cost of sedation management and (3) the quality of a child's life and emotional health after hospital discharge.

Children who require intensive care and a ventilator also receive sedative medication to keep them comfortable and safe. In contrast to these benefits, we know that the more sedation is used, the longer it takes for a child to get off the ventilator which increases their risk for complications (for example, developing pneumonia on the ventilator).

Recent studies in adult intensive care have shown that when doctors and nurses work together as a team and use a guideline to manage sedation, patients come off the ventilator faster with fewer side effects. This strategy includes doctor and nurse training and agreement on which sedatives are used when patients are on ventilators, having doctors and nurses jointly identify a daily sedation goal for a patient, having nurses use a plan to guide changes in a patient's sedatives based on that goal, and keeping track of patient care so that doctors and nurses can evaluate how well they manage a patient's sedation. The information we have on this strategy shows that most adult patients have good control of their pain and anxiety and that they have no memory of waking up from sedation after they are sent home from the hospital.

We have preliminary information that shows that a pediatric sedation management guideline may also be helpful in caring for children on ventilators. Currently it is impossible to know for certain the best way to keep children comfortable and safe while on a breathing machine unless we compare one group of children whose sedation is managed in the usual way to one group of children whose sedation is managed with the proposed pediatric sedation management guideline.

Approximately 26 pediatric intensive care units are working together to evaluate a pediatric sedation management guideline in children who need to be on ventilators to support their breathing and following up on these children after hospital discharge.

About half of the intensive care units will be randomly selected (by chance) to train doctors and nurses to use the pediatric sedation management guideline.

About half of the intensive care units will be randomly selected (by chance) to continue what they normally do and not change the way doctors and nurses manage sedation.

The aim of this study is to conduct a multicenter clinical trial to test whether pediatric patients with acute respiratory distress managed with the pediatric sedation management guideline experience better outcomes than patients receiving usual care.

How long will I be in the study? How many other people will be in the study?

You are being asked to allow our research team to contact you once 6 months after discharge from the pediatric intensive care unit (PICU). For this follow up part of the study, we will randomly (by chance) select about half of the families who have agreed to participate in this part of the study and invite them to take part in a mailed survey and telephone-based interview conducted by the CRISMA center (Clinical Research, Investigation, and Systems Modeling of Acute Illness center) at the University of Pittsburgh.

We plan to enroll almost 2,900 children (between 2 weeks and 18 years of age) in approximately 26 different pediatric intensive care units. We expect to enroll approximately ____ children from this intensive care unit.

What am I being asked to do?

If you agree, we will send a copy of this consent form and some information about you to our research team at the CRIMSA research team at the University of Pittsburgh for the follow up part of the study. If selected, personnel from the CRIMSA research team will contact you six months after you are discharged from the PICU and send you two surveys in the mail that ask you some questions about how you feel. You can either fill them out and mail them back or complete them on the internet. This would happen once and take about 10 minutes for you to answer the questions. They will also call on the telephone to talk with your parents about how things are going and to see if you have any questions about the surveys.

If you choose not to participate we will not contact you for a follow-up interview.

What are the possible risks or discomforts?

If you are selected to participate in this study, there is a risk of possible discomfort in answering questions on the survey. To minimize this risk, you will be provided a copy of the survey beforehand, and you will be given the option to skip questions or end the conversation at any time. If the CRISMA team determines that you meet the criteria for Post-Traumatic-Stress Disorder (PTSD), they will inform the study doctor so that appropriate referrals and/or follow-up can be made.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You are not expected to get any benefit from being in this research study. Future children who receive sedation in the ICU and their families may benefit from this study, which will provide a better understanding of how best to use sedatives in children on ventilators.

What other choices do I have if I do not participate?

If you choose not to participate, you will not be contacted for the follow-up part of this study.

Will I be paid for being in this study?

You will not be paid for being in this study.

Will I have to pay for anything?

There will be no cost to you to be in this research study.

What happens if I am injured or hurt during the study?

All forms of medical diagnosis and treatment involve some risk of injury. In spite of all precautions, you might develop an injury from participating in this study. If such injuries arise, we will help you get reasonable, immediate, and necessary medical care for your injury. Reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, our research staff will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

Additionally, we are not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

When is the Study over? Can I leave the Study before it ends?

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

This study is expected to end after all information has been collected and reviewed. This study may also be stopped at any time by your doctor, the study Principal Investigator and the study Sponsor (National Institutes of Health) without your consent because it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.

You may also be removed from the research study by the Principal Investigator if, for example, the CRISMA researchers cannot get in touch with you to conduct the follow-up part of study.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The information we obtain for the study will be sent to the University of Pennsylvania School of Nursing (Lead Center), the Children's Hospital, Boston (Data Coordination Center), CRISMA Center at the University of Pittsburgh (Coordinating patient Follow up), and the National Institutes of Health (Sponsor). They will be examining the research records for quality assurance and data analysis.

All information sent to the University of Pennsylvania School of Nursing and the Data Coordination Center at Children's Hospital, Boston will not have any of your identifying information on it.

If you agree to participate in the follow up part of this study, a copy of this signed consent form along with demographic and contact information will be sent directly to the CRISMA Center at the University of Pittsburgh. Information will be sent via secure FAX or encrypted e-mail. All data will be secured for the purpose of confidentiality, and data will be used only for research purposes. The only dataset with subject identifier information will be the subject tracking system used to follow-up and contact families. All other datasets will label subject records with a unique study number and be stripped of other identifying information.

What information about me may be collected, used or shared with others?
This part of the form gives more detailed information about how your personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

- Name, address, telephone number, date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Authorized personnel at **[NAME OF CENTER]**

Who, outside of the [NAME OF CENTER], might receive my information?

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness Center) at the University of Pittsburgh (the follow-up coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor

Oversight organizations

- The Office of Human Research Protections
- The study data and safety monitoring board

Once your personal health information is disclosed to others outside the **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your privacy.

How long may the [NAME OF CENTER] use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the **[NAME OF CENTER]** may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The **[NAME OF CENTER]** Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Nursing to use your personal health information collected for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Nursing to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this informed consent and HIPAA authorization form will be given to you. You will also be given the University of Pennsylvania Health System and School of Nursing's Notice of Privacy Practices that contains more information about the privacy of your health information.

Consent

_____	_____	_____
Name of Subject (Please Print)	Signature of Subject	Date

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

G. HIPAA Authorization – Core

Research Subject HIPAA Authorization
TEMPLATE – Core Phase of Study Only

Protocol Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure (RESTORE) - **Core Phase of Study Only**

Principal Investigator:

Emergency Contact:

You have agreed to participate in the study mentioned above and have signed or will sign a separate informed consent that explains the procedures of the study and the risks and benefits of participation. This authorization form gives more detailed information about how your personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

What personal health information is collected and used in this study, and might also be disclosed?
The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is your personal contact and health information being used?
Your personal health information and results of tests and procedures are being collected as part of this research study.

Which of our personnel may use or disclose your personal health information?
The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the **[NAME OF CENTER]**, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring).

Who, outside of [NAME OF CENTER], might receive your personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your DE-IDENTIFIED personal health information. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness center)at The University of Pittsburgh (the follow-up coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor
- Others as appropriate

Regulatory and safety oversight organizations

- The Office of Human Research Protections
- The study Data and Safety Monitoring Board

Once your personal health information is disclosed to others outside of **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your privacy.

How long may [NAME OF CENTER] be able to use or disclose your personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research repository (database). However, [NAME OF CENTER] may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The **[NAME OF CENTER]** Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your records?
During your participation in this study, you will be able to access your medical records.

Can you change your mind?
Yes, at any time you may withdraw your approval to allow the use and disclosure of your personal health information as described here. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the **[NAME OF CENTER]** to use and disclose personal health information collected about you for research purposes as described above.

_____
Name of Subject (PRINT)

Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date
Name of Person Obtaining Authorization (PRINT)	Signature	Date

H. HIPAA Authorization – Core and Follow Up

Research Subject HIPAA Authorization
TEMPLATE

Protocol Title:	Sedation Management in Pediatric Patients with Acute Respiratory Failure (RESTORE) – **Core and Follow-Up Phase of Study**
Principal Investigator:	
Emergency Contact:	

You have agreed to participate in the study mentioned above and have signed or will sign a separate informed consent that explains the procedures of the study and the risks and benefits of participation. This authorization form gives more detailed information about how your personal health information may be used and disclosed by **[NAME OF CENTER]** and the individual Principal Investigator, subject to **[NAME OF CENTER]** procedures.

What personal health information is collected and used in this study, and might also be disclosed?
The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth
- Personal medical history
- Current medications and therapies
- Information from the medical record related to physical examination and results of tests and procedures

Why is your personal contact and health information being used?
Your personal health information and results of tests and procedures are being collected as part of this research study.

Which of our personnel may use or disclose your personal health information?
The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the **[NAME OF CENTER]**, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring).

Who, outside of [NAME OF CENTER], might receive your personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- The University of Pennsylvania School of Nursing (the lead coordinating center)
- Children's Hospital Boston (the lead data coordinating center)
- The CRISMA Center (Clinical Research, Investigation, and Systems Modeling of Acute Illness center) at The University of Pittsburgh (the follow-up coordinating center)
- The funding sponsor (National Institutes of Health) and organizations supporting the sponsor
- Others as appropriate

Regulatory and safety oversight organizations

- The Office of Human Research Protections
- The study Data and Safety Monitoring Board

Once your personal health information is disclosed to others outside of **[NAME OF CENTER]**, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to **[NAME OF CENTER]** procedures developed to protect your privacy.

How long may [NAME OF CENTER] be able to use or disclose your personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research repository (database). However, **[NAME OF CENTER]** may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The **[NAME OF CENTER]** Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your records?
During your participation in this study, you will be able to access your medical records.

Can you change your mind?
Yes, at any time you may withdraw your approval to allow the use and disclosure of your personal health information as described here. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the **[NAME OF CENTER]** to use and disclose personal health information collected about you for research purposes as described above.

_____
Name of Subject (PRINT)

Name of Parent/Legal Guardian (Please Print)	Signature of Parent/Legal Guardian	Date
Name of Person Obtaining Authorization (PRINT)	Signature	Date

Appendix II: RESTORE Nurse-Implemented Goal-Directed Comfort Algorithm

PROVIDED FOR SITES RANDOMIZED TO INTERVENTION ARM ONLY

Appendix III. Summary of Mock Screening from Participating Sites

Center	Mgmt	# PICU Beds	ADC	Intubated & Ventilated Pts/mo in Screen	Elig Pts/mo in Mock Screen	Venti-lated Pts/yr	ICU Fellows	Nurse FTE	% Med	Size (Mock screen) *
Advocate	Closed	15	12	18	4	233	Yes	38	71%	Small 4-6
Oakland	Open	23	16	28	17	395	Yes	70	41%	Large 10+
UCSF	Closed	14	10.8	26	6	271	Yes	41	52%	Small 4-6
Alabama	Open	19	11.8	48	15	472	Yes	69	46%	Large 10+
CHOP	Open	45	37.1	47	8	1218	Yes	134	53%	Small 4-6**
Chicago	Closed	42	34.2	72	15	408	Yes	127	82%	Large 10+
Kansas City	open	27	18	89	9	923	No	95	56%	Medium 7-9
Michigan	Open	16	14.4	25	4	365	Yes	54	52%	Small 4-6
Dartmouth	Open	10	8	8	5	120	No	19	60%	Small 4-6
Portland	Open	16	11.2	30	8	408	No	44	39%	Medium 7-9
Duke	Closed	29	17.3	81	13	407	Yes	60	50%	Large 10+
Hopkins	Closed	26	20	32	7	648	Yes	79	31%	Medium 7-9
Stanford	Open	12	12	30	4	295	Yes	43	48%	Small 4-6
Vanderbilt	Open	36	19.2	59	16	895	Yes	77	51%	Large 10+
Al duPont	Closed	22	15.9	36	9	340	Yes	49	54%	Medium 7-9
Primary	Open	32	21	65	16	1013	Yes	118	41%	Large 10+
St Louis	Open	24	16	40	15	639	Yes	80	55%	Large 10+
UMass	Closed	7	7	11	6	106	No	30	64%	Small 4-6
UCDavis	Open	16	14	34	5	539	No	67	65%	Small 4-6
Maryland	Closed	28	14	24	9	177	Yes	40	63%	Medium 7-9
Yale	Closed	19	10.3	unavailable	9	296	Yes	39	64%	Medium 7-9
Connecticut	Open	18	10.8	48	10	312	No	47	44%	Medium 7-9

* Randomization strata (small, medium, and large PICUs) will be reconfirmed during baseline period.

Appendix IV. Project Timeline

An overview of the project timeline is presented below. During year 1, the primary focus will be on the production of program material and training of study personnel. Years 2 to 4 represent patient enrollment. The focus of Year 5 will be on final data analysis and preparation of reports and manuscripts.

	Year 1				Year 2				Year 3				Year 4				Year 5
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1-4
Finalizing CRFs																	
Building web-based data entry system																	
Educational materials																	
Videotape production																	
Baseline training																	
Baseline data collection																	
Start-up meeting																	
Site training (intervention)																	
Intervention or continued baseline DC																	
PI site visit (intervention sites)																	
Auditor site visits																	
DSMB meeting																	
Data cleaning																	
Data analysis																	
Preparation of reports																	
Manuscript preparation																	