# Clinical Effectiveness of the "PICU Up!" Multi-faceted Early Mobility Intervention for Critically Ill Children: A Pragmatic, Stepped-wedge Trial

| | |
|---|---|
| **ClinicalTrials.gov Protocol Identifier:** | NCT04989790 |
| **Trial Principal Investigator:** | Sapna R. Kudchadkar, MD, PhD |
| **Trial Lead Statistician:** | Elizabeth Colantuoni, PhD |
| **Funded by:** | The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, US |
| **Version Number:** | 2.0 |
| **Version Date:** | May 12, 2026 |

**SIGNATURE PAGE AND APPROVALS**

I acknowledge that I have reviewed and approved the document referenced above.

**Elizabeth Colantuoni, PhD**
Lead Biostatistician
Johns Hopkins University
Baltimore, MD

Signature 

Date 5/12/2026

**Sapna R. Kudchadkar, MD, PhD**
Principal Investigator
Johns Hopkins University
Baltimore, MD

Signature 

Date 5/12/2026

# Contents

List Of Abbreviations ..... 3
**1. STATISTICAL ANALYSIS PLAN REVISIONS** ..... 4
**2. PROTOCOL SUMMARY SYNOPSIS** ..... 4
**5. STUDY ENDPOINTS** ..... 5
3.1 Primary Outcome ..... 5
3.2 Secondary effectiveness outcomes ..... 6
3.3. Exploratory outcomes ..... 6
3.3 Performance outcomes ..... 7
3.4 Safety outcomes ..... 7
**4 Sample Size and Power** ..... 7
**5. Definitions and principles for the statistical analysis** ..... 8
5.1 Study population definition ..... 8
5.2 Treatment effect definition ..... 8
5.3 Multiplicity ..... 8
5.4 Statistical significance ..... 8
5.5 Missing data ..... 8
**6. Statistical methods** ..... 8
6.1 Demographic and Baseline Clinical Characteristics ..... 8
6.2 Analysis of Primary Outcome ..... 9
6.2.1 Primary Analysis of Primary Outcome ..... 9
6.2.2 Secondary Analyses of Primary Outcome ..... 9
6.2.3 Subgroup Analyses of Primary Outcome ..... 9
6.3 Analysis of Secondary Outcomes ..... 10
6.4 Analysis of Exploratory Outcomes ..... 10
6.5 Process evaluation ..... 10
6.6 Safety outcomes ..... 10
References ..... 11

# List Of Abbreviations

PICU Up! - pragmatic, interprofessional and multifaceted early mobility intervention
PICU – Pediatric Intensive Care Unit
ECMO - Extracorporeal Membrane Oxygenation
SAP – Statistical Analysis Plan
CCC – Clinical Coordinating Center
DCC – Data Coordinating Center
DSMB - Data Safety Monitoring Board
PI – Principal Investigator
AVF – Alive and Free of Ventilation
DNR – Do Not Resuscitate
DNI – Do Not Intubate
CPR – Cardiopulmonary Resuscitation
ADCF – Alive and Delirium and Coma Free
ACF – Alive and Coma Free
ITT – Intention To Treat
PRISM Illness Severity Score – Pediatric Risk of Mortality Illness Severity Score

## 1. STATISTICAL ANALYSIS PLAN REVISIONS

The following revisions were made:

- Section 6.6 was revised to reflect that safety outcomes were only recorded by the sites during the implementation period. This section originally stated that comparisons between safety outcomes reported during the pre- and post-implementation periods would be made.

## 2. PROTOCOL SUMMARY SYNOPSIS

**Title:** Clinical Effectiveness of the "PICU Up!" Multifaceted Early Mobility Intervention for Critically Ill Children: A Pragmatic, Stepped-wedge Trial

**Short Title:** The PICU Up! Stepped-wedge Trial

**Study Description:** This study is a mixed-methods, stepped-wedge, cluster randomized trial of a pragmatic, interprofessional and multifaceted early mobility intervention (PICU Up!) conducted in 10 hospitals. Over a 2-year period, data will be collected on 1,440 PICU patients. The study includes an embedded process evaluation to identify factors associated with reliable PICU Up! adoption and performance. All participating PICUs will simultaneously start the control period with data collection, and conduct implementation planning for the PICU Up! intervention, a multifaceted, interprofessional and systematic tiered pathway that is integrated into routine PICU practice to safely optimize early and progressive mobility. The order in which the PICUs will move into the intervention period will be determined through randomization. Data collection will occur only during control and intervention phases (not during implementation phase). Data collection includes patient demographic, clinical, and rehabilitation data from the electronic health record (EHR) from PICU admission through Day 21 or PICU discharge, whichever occurs first.

**Study Population:** As a pragmatic trial, all PICU patients regardless of their length of stay, are screened for the PICU Up! unit-based intervention, which includes criteria for exclusion based on specific clinical factors (i.e., open chest or abdomen, ECMO).(1) Criteria for inclusion in data collection and statistical analysis are children receiving invasive mechanical ventilation ≥48 hours on Day 3 of PICU admission (n=1,440).

**Primary Objective:** To evaluate if the PICU Up! intervention, delivered in real-world conditions, decreases mechanical ventilation duration (primary outcome) and improves delirium and functional status compared to usual care in critically ill children. Our hypothesis is that PICU Up! (vs. usual care) will shorten the duration of mechanical ventilation resulting in an increase of at least 1.8 days alive and ventilator free during the 21-day follow-up.

**Secondary Objectives:**

- To evaluate if the PICU Up! Intervention, delivered in read-world conditions, improves the following outcomes at the earlier of PICU discharge or day 21: delirium (defined as days alive, and delirium- and coma-free), functional status (Functional Status Scale, Pediatric Cerebral Performance Category and Pediatric Overall Performance Category), deep sedation (defined as days alive and coma free), PICU length of stay, PICU mortality,

new pressure injury, and opioid and benzodiazepine exposure (median mg/kg/day; in morphine- and benzodiazepine equivalents).
- The trial will also evaluate PICU and hospital disposition (discharge to home/inpatient floor/inpatient rehabilitation/other hospital)

3. To evaluate the proportion of PICU Up! Elements performed as a measure of reliable PICU Up! delivery

## 4. INTRODUCTION

This Statistical Analysis Plan (SAP) provides the details of statistical considerations, analyses, and reports planned for the PICU Up! Stepped-wedge trial, including proposed statistical models, sample size estimates, power considerations, and safety analyses. In addition, this plan will define the analysis populations and specify which population will be used for the primary analyses. It will define secondary, sensitivity and exploratory analyses.

The Clinical Coordinating Center (CCC, Chair: Sapna Kudchadkar, MD, PhD) and Data Coordinating Center (DCC, Chair: Dale M. Needham, MD, PhD) at the Johns Hopkins University has the primary responsibility for data quality and creating analytical datasets and creating Data and Safety Monitoring Board (DSMB) reports.

Statistical analyses will be performed on data that have been quality-assured through DCC protocols and monitoring reviews (including repeated remote site monitoring visits throughout the study duration), and that have been exported directly from the REDCap database.

All data collection procedures and statistical analyses described in this SAP were finalized and approved by the PICU Up! Stepped wedge trial Principal Investigator (PI) and Lead Statistician. The data collection procedures and statistical analyses described herein apply specifically to the methods that will be used on the data reported in the primary manuscript upon completion of the clinical trial. These procedures and analyses may be modified and are given precedence over the analytical plans outlined in the clinical protocol; however, any major modifications or changes in the primary endpoint and/or its analysis will also be reflected in a protocol amendment. Any updates to the SAP will be thoroughly detailed and documented in later SAP versions.

## 5. STUDY ENDPOINTS

### 3.1 Primary Outcome

We will consider Time 0 as the time of endotracheal intubation or PICU admission for patients intubated at an outside hospital. Days alive and free of ventilation (AVF) are counted following the first time the endotracheal tube was <u>continuously</u> absent for at least 24 hours. Days AVF are counted for <u>both</u> patients who die prior to or survive through Day 21. Patients will be assigned 0 days AVF if they remained intubated through 21 days or are intubated at the time of transfer to another PICU prior to Day 21. Days following discharge without a tracheostomy or with only a tracheostomy will count as days alive and ventilator free. Patients that meet exclusion criteria during follow-up will

be assigned no ventilator free days from the day of exclusion to Day 21. The exclusion criteria include: new active limitation of care orders (i.e. DNR, DNI, no CPR, etc.), brain death evaluation, open chest or abdomen, ECMO support. Ventilator status was carried forward for patients who were intubated on Day 2 or 3 of follow-up and still in the PICU on Day 21, i.e. these patients have 20 or 19 days of follow-up prior to Day 21, respectively, for calculation of days AVF.

We purposefully chose days AVF as the primary outcome given the abundance of literature suggesting the negative impact prolonged mechanical ventilation has on critically ill children's outcomes and established association with sedative exposure, delirium, and ICU-acquired morbidities. We chose days AVF instead of duration of mechanical ventilation due the challenge of analyzing duration of mechanical ventilation in the presence of patient mortality, which could introduce bias in our analysis if not appropriately accounted for. For example, standard survival analysis methods would treat patient mortality as an independent censoring event for duration of mechanical ventilation, even though these outcomes are likely correlated. Days AVF was chosen over the alternative composite "alive and ventilator free days" as days AVF considers any day off the ventilator as important to the patient, family and provider regardless of whether the patient ultimately survivors or not; whereas the latter more heavily focuses on mortality by assigning a value of 0 to all patients that die regardless of duration of mechanical ventilation. Additionally, we chose this primary outcome in lieu of PICU length of stay due to hospital capacity factors that may delay PICU discharge: even if a patient is ready to be transferred to the inpatient floor, they may remain in the PICU not due to clinical necessity, but due to a lack of inpatient beds. Tracheotomy with ongoing mechanical ventilation will count as mechanical ventilation days, just as occurs with endotracheal intubation with mechanical ventilation.

### 3.2 Secondary effectiveness outcomes

Secondary outcomes include:

- Days alive and delirium and coma free (ADCF) to Day 21, which will be supplemented with evaluation of days alive and coma free (ACF) and days alive. If the patient was discharged from the PICU alive, all days following PICU discharge will be considered days alive, delirium- and coma-free. If the patient satisfies an exclusion criteria (see Section 3.1 above), all days following meeting the exclusion criteria will be defined as coma days.
- Functional status at the sooner of PICU discharge or Day 21 (Functional Status Scale, Pediatric Cerebral Performance Category and Pediatric Overall Performance Category).

### 3.3. Exploratory outcomes

Exploratory outcomes include:

- PICU length of stay (through Day 21)
- PICU mortality (through the earlier of PICU discharge or Day 21)
- PICU and hospital disposition (discharge to home/inpatient floor/inpatient

rehabilitation/other hospital)
- Presence of a new pressure injury (through the earlier of PICU discharge or Day 21)
- Opioid exposure (median mg/kg/day; morphine equivalents) (through the earlier of PICU discharge or Day 21)
- Benzodiazepine exposure (median mg/kg/day; benzodiazepine equivalents) (through the earlier of PICU discharge or Day 21)

### 3.3 Performance outcomes

We will define individual patient PICU Up! performance as the proportion of each eligible element completed divided by the number of eligible elements for the patient, through PICU discharge or Day 21. We will summarize the outcome of PICU Up! performance at the PICU level for each month of the intervention period. Specifically, we will calculate a measure of complete, proportional, and individual element performance for each PICU. The monthly complete and proportional performance will respectively be defined as the proportion of patient days (for eligible patients) in which every eligible element of PICU Up! was performed and the proportion of eligible elements received divided by the number of eligible elements. Individual element performance will be defined as the proportion of patient days (for eligible patients) where the individual element was received divided by the number of days where the individual element was eligible.

### 3.4 Safety outcomes

All patients will be closely monitored as part of routine ICU care. Each site will document the following events of interest and determine if they meet prespecified criteria for suspected, unexpected, serious adverse reaction: unplanned extubation or device removal, falls and cardiac arrest.

## 4 Sample Size and Power

Utilizing site-specific admissions data, the *PARK-PICU* point-prevalence study's screening and clinical data, and data from our pilot multicenter PICU Up! trial, we anticipate that, conservatively, an average of 8 patients/cluster/month will be eligible for inclusion in data collection (mechanically ventilated ≥48h on PICU Day 3 and meeting rest of eligibility criteria). In the stepped-wedge design proposed, with two hospitals switching at each step, there will be a total of 180 months of observation (90 months control/90 months intervention). Thus, there will be 720 patients included in the baseline period and 720 patients included in the intervention (post-implementation) period. Using preliminary data obtained from our multicenter pilot trial, we simulated 1000 hypothetical stepped-wedge trials allowing the days AVF to day 21 to decline linearly over time (Month 1 mean (variance) of 13.2 (26.4) days AVF to day 21, with monthly decline of 0.1 days) with a fixed decline (i.e. effect of intervention is constant over time) at both the start of the implementation period and during the intervention period. To account for clustering of patients within hospitals, we assumed that patients within hospitals will be correlated with an ICC of 0.01, based on data from our pilot multicenter PICU Up! trial. Given the design, the anticipated sample size and a 5% Type I error rate, we will have 80% power to detect at least a 1.8 day improvement in the mean days AVF to day 21 comparing the intervention and control period. A one to two-day reduction in duration of mechanical ventilation is supported by the literature as clinically meaningful[1-3].

## 5. Definitions and principles for the statistical analysis

In this section, the definitions and principles for the statistical analysis are presented.

### 5.1 Study population definition

All analyses will be conducted in accordance with the intention-to-treat (ITT) principle. The ITT population will be all subjects enrolled.

### 5.2 Treatment effect definition

We will define and estimate the patient-average treatment effect. That is, we will compare the average outcome among eligible patients following PICU-Up! implementation to the average outcome among eligible patients during the control period. The patient-average treatment effect answers the question: how effective is the PICU Up! intervention for the average patient. Alternatively, we could focus on the cluster-average treatment effect. This approach compares the cluster average outcome following PICU-Up! implementation to the cluster average outcome during the control period. The cluster-average treatment effect answers the question: how effective is the PICU Up! intervention for the average cluster of patients.

### 5.3 Multiplicity

There will be no correction for multiplicity. The primary outcome consists of only one measure (days alive and ventilator free) and therefore does not require multiple group comparisons. No hypothesis testing will be performed for the secondary outcomes, but rather differences in mean secondary outcomes across the time periods will be estimated and statistical uncertainty will be quantified by 95% confidence intervals.

### 5.4 Statistical significance

Statistical significance will be set at $p$-value < 0.05 using a two-sided hypothesis test for the primary outcome analysis; all secondary analyses will be considered exploratory with two-sided 95% confidence intervals reported.

### 5.5 Missing data

We will estimate the proportion of missing values for all the baseline demographic and clinical characteristics, as well as for the primary and secondary outcomes, both overall and stratified by pre- and post- PICU Up! implementation. Mean or mode replacement will be used for variables that have proportion missing ≤ 5%. If the proportion of missing data exceeds 5%, we will employ multiple imputation using chained equations to impute the missing values. Multiple imputed datasets will be generated, m = 100, and the results of an analysis will be the pooled across the multiple imputed datasets using Rubin's method. We anticipate more than 5% missing values for daily delirium assessments. Given this expectation, we will use multiple imputation using chained equations to impute missing daily delirium status. The models for daily delirium status will be fit separately for the pre- and post- PICU Up! implementation, and include age, sex and study month, the prior day's sedation and delirium score, and current day's sedation score and dose of continuous infusion of sedative and opioids.

## 6. Statistical methods

### 6.1 Demographic and Baseline Clinical Characteristics

Demographics (including age, sex, race), and baseline clinical characteristics (including

admission weight and height, and source and reason for PICU admission) will be summarized using descriptive statistics for patients observed under the baseline, implementation, and intervention periods.

### 6.2 Analysis of Primary Outcome

#### 6.2.1 Primary Analysis of Primary Outcome

Using the ITT population, the effect of the PICU Up! intervention on days AVF will be estimated using a linear model that includes an indicator for the intervention (post-implementation) vs. control periods and a fixed effect of calendar time (defined as month counting from the start of the control period to the last month of the study, modeled as a natural cubic spline) to account for temporal trends in the outcomes over the period of the study. To account for clustering of participants within PICUs, robust variance estimates will be used. The estimated coefficient for the indicator of intervention vs. control period represents the patient-average treatment effect, i.e. the mean difference in days AVF by day 21 comparing the intervention and control period. Our analysis approach was selected to provide valid estimates of the patient-average treatment effect in the event of informative-cluster size, i.e. when the outcome is correlated with the number of eligible patients in the participating PICUs.

#### 6.2.2 Secondary Analyses of Primary Outcome

The primary analysis for the primary outcome will be unadjusted, that is, we will assume that patients enrolled in the study over time will be similar with respect to characteristics associated with the outcomes (e.g., age and severity of illness). Secondary analysis of the primary outcome will include exploratory analyses to evaluate this assumption, and the linear model described above will be extended to include adjustment for the following baseline patient characteristics expected to be prognostic of VFDs: age, admission diagnosis category (medical vs. surgical), baseline Pediatric Cerebral Performance Category (normal vs. not normal), Pediatric Overall Performance Category (normal vs. not normal), Functional Status Scale (normal vs. not normal) and PRISM illness severity (low risk (0-10), moderate risk (11-20), high risk (21-30), and very high risk (>30)).

In addition, we will consider two alternative definitions for the patient-average treatment effect. We will estimate the mean difference in days AVF by day 21 during i) the first 6-months post-implementation and ii) the last 6-months post-implementation to the control period. A separate linear models will be used to estimate these treatment effects; one will include indicators that partition the post-implementation period into the first 6 months vs. otherwise and the other will include indicators that partition the post-implementation period into the last 6-months vs. otherwise.

#### 6.2.3 Subgroup Analyses of Primary Outcome

The patient-average treatment effect will be estimated separately among the following pre-specified subgroups by extending the linear model described for the primary analysis to include main effect of the subgroup variable and interactions of the subgroup variable with the fixed effects for the implementation and intervention periods. The model fit will be used to estimate the subgroup patient-average treatment effects with corresponding 95% confidence intervals. The subgroups include: sex, age (0-2, 3-6, 7-12, 13-18 and >18 years of age), Admission type

(medical vs. surgery), Functional Status Scale (normal vs. not normal) and PRISM illness severity (low risk(0-10), moderate risk (11-20), high and very high risk (>20 with >30 indicating very high risk).

### 6.2.4 Sensitivity Analyses of Primary Outcome

As a sensitivity analysis, we will repeat the analyses described in Sections 6.2.1 through 6.2.3 using an alternative definition of the primary outcome: days AVF through day 19. This will allow for 19 days of follow-up for each patient and no imputation of last day of follow-up ventilation status carried forward.

### 6.3 Analysis of Secondary Outcomes

The same primary, secondary, and subgroup analyses describe above will be applied to the secondary outcomes. Linear regression models will be used for continuous and count secondary outcomes, e.g. days ADCF, days ACF and days alive to Day 21.

For the ordinal secondary outcomes, Functional Status Scale, Pediatric Cerebral Performance Category and Pediatric Overall Performance Category, we will collapse the ordered categories into normal vs. mild/moderate vs. severe and very severe dysfunction for the Functional Status Scale, and normal vs. not normal for the Pediatric Cerebral and Overall Performance Category variables. We will utilize multinomial or logistic regression models to evaluate the effect of the intervention. The models will include the same fixed effects as described for the primary analysis of the primary outcome. Robust variance estimates will be used to account for clustering of patients within site. From the fit of the multinomial and logistic models, we will estimate the absolute difference in the probability of each ordered category comparing the intervention and baseline period.

### 6.4 Analysis of Exploratory Outcomes

The exploratory outcomes, all measured to the first of PICU discharge or 21 days after PICU admission, include PICU length of stay, PICU mortality, PICU and hospital disposition, presence of a new pressure injury, opioid exposure (median mg/kg/day; morphine equivalents), benzodiazepine exposure (median mg/kg/day; benzodiazepine equivalents). Linear models as described for the primary analysis of the primary outcome will be applied to continuous or count exploratory outcomes. Logistic regression models, as described for the analysis of secondary outcomes, will be applied to binary exploratory outcomes.

### 6.5 Process evaluation

Trends in performance with the PICU Up! intervention within a PICU post-implementation will be explored using spaghetti plots with locally weighted regression smoothers to explore the general trends over time across all PICUs. Poisson models will be used to model the trends in performance over time via restricted cubic splines; robust variance estimates will be used to account for clustering of patients within PICUs. In addition, we will summarize patterns of delirium and sedation screening during both the control and post-implementation using visual displays and Poisson models.

### 6.6 Safety outcomes

We will summarize the rates of safety outcomes, including unplanned extubation or device removal, falls and cardiac arrest, recorded during the implementation periods using descriptive statistics and data visualizations.

**References**

1. Curley MA, Wypij D, Watson RS, Grant MJ, Asaro LA, Cheifetz IM, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA. 2015;313(4):379-89.
2. Saelim K, Chavananon S, Ruangnapa K, Prasertsan P, Anuntaseree W. Effectiveness of Protocolized Sedation Utilizing the COMFORT-B Scale in Mechanically Ventilated Children in a Pediatric Intensive Care Unit. J Pediatr Intensive Care. 2019;8(3):156-63.
3. Dreyfus L, Javouhey E, Denis A, Touzet S, Bordet F. Implementation and evaluation of a paediatric nurse-driven sedation protocol in a paediatric intensive care unit. Ann Intensive Care. 2017;7(1):36.