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Design and rationale of the Post-Intensive Care Syndrome – paediatrics (PICS-p) Longitudinal Cohort Study

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ABSTRACT

Introduction As paediatric intensive care unit (PICU) mortality declines, there is growing recognition of the morbidity experienced by children surviving critical illness and their families. A comprehensive understanding of the adverse physical, cognitive, emotional and social sequelae common to PICU survivors is limited, however, and the trajectory of recovery and risk factors for morbidity remain unknown.

Methods and analysis The Post-Intensive Care Syndrome – paediatrics Longitudinal Cohort Study will evaluate child and family outcomes over 2 years following PICU discharge and identify child and clinical factors associated with impaired outcomes. We will enrol 750 children from 30 US PICUs during their first PICU hospitalisation, including 500 case participants experiencing ≥3 days of intensive care that include critical care therapies (eg, mechanical ventilation, vasoactive infusions) and 250 age-matched, sex-matched and medical complexity-matched control participants experiencing a single night in the PICU with no intensive care therapies. Children, parents and siblings will complete surveys about health-related quality of life, physical function, cognitive status, emotional health and peer and family relationships at multiple time points from baseline recall through 2 years post-PICU discharge. We will compare outcomes and recovery trajectories of case participants to control participants, identify risk factors associated with poor outcomes and determine the emotional and social health consequences of paediatric critical illness on parents and siblings.

Ethics and dissemination This study has received ethical approval from the University of Pennsylvania Institutional Review Board (protocol #843844). Our overall objective is to characterise the ongoing impact of paediatric critical illness to guide development of interventions that optimise outcomes among children surviving critical illness and their families. Findings will be presented at key disciplinary meetings and in peer-reviewed publications at fixed data points. Published manuscripts will be added to our public study website to ensure findings are available to families, clinicians and researchers.

Trials registration number NCT04967365.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Post-Intensive Care Syndrome – paediatrics (PICS-p) Longitudinal Cohort Study will comprehensively characterise post-paediatric intensive care unit (PICU) recovery in children and their families to facilitate the development of targeted interventions that prevent or mitigate adverse outcomes.

⇒ By comparing critically ill children receiving ≥3 days of intensive care to control participants who spend a single night in the PICU without intensive care therapies, we will better understand the contribution of critical illness itself to adverse outcomes while also exploring whether there are common sequelae in all children or families who experience the PICU environment regardless of illness severity or exposure duration.

⇒ While exclusion of children with prior intensive care unit admissions limits generalisability, this will allow us to explore the phenomenon of PICS-p from its onset and capture the development of chronic critical illness.

⇒ Although parent proxy-report and self-report of pre-PICU baseline may be affected by recall bias, anchoring assessment of change on pre-illness baseline will allow us to characterise the magnitude and direction of change for each measure and explore factors associated with both decline and improvement.

⇒ While enrolment is limited to families in the USA who speak English or Spanish, we will evaluate for differences in recruitment, retention and outcomes by race, ethnicity, language, social influencers of health and geography to understand how these factors may affect generalisability across populations.

INTRODUCTION

Survival following paediatric critical illness has improved substantially over the past several decades, with mortality now <3% of all paediatric intensive care unit (PICU) admissions.[1–4] As PICU mortality declines, there is increasing recognition of the morbidity experienced by children surviving critical illness and their families.[5–8] Impairments in health-related quality of life (HRQL), overall health, physical function, neurocognition, emotional health and social development and relationships have been identified in PICU survivors.[9–17] Families of these children

also experience deficits in mental health, quality of life and family cohesion.[18–22]

Despite increasing attention to survivor outcomes, a comprehensive understanding of PICU morbidity and the trajectory of recovery among PICU survivors remains limited. Most existing studies have focused on narrow patient populations, examined isolated outcome domains or assessed recovery at a single time point,[23] limiting our understanding of common morbidities facing the PICU population and how different sequelae intersect with each other. With studies rarely considering the impact of children's pre-existing health status or clinical factors on outcomes, it is difficult to identify the extent to which different elements of critical illness and PICU admission contribute to post-PICU morbidity.

In adult survivors of critical illness, increasing awareness of new morbidities across multiple health domains led to the development of the concept of post-intensive care syndrome (PICS).[24] Post-intensive care syndrome in paediatrics (PICS-p) built on this framework integrating the child's pre-illness baseline, the PICU experience for the child and family, ongoing child and family development and varying trajectories of recovery that can potentially span decades.[7] Applicability of the PICS-p conceptual framework to the actual patient experience requires validation. Targeting interventions to address PICU morbidity requires an understanding of the risk factors, the health domains most impacted and the recovery trajectory among children and families who share the PICU experience.

In this study, Post-Intensive Care Syndrome – paediatrics Longitudinal Cohort Study, we will address these knowledge gaps by evaluating child and family outcomes over 2 years following PICU discharge to characterise trajectories of recovery and identify risk factors associated with impaired outcomes in multiple health domains. We will enrol 750 children during their first PICU hospitalisation, including 500 'case' participants exposed to intensive care therapies and ≥3 days of intensive care and 250 'control' participants experiencing one night in the PICU with no intensive care therapies. Outcomes in multiple health domains for children, parents and siblings for 2 years following PICU discharge will be compared between case and control participants. This work will elucidate the ongoing impact of paediatric critical illness and guide future interventions to optimise outcomes.

METHODS AND ANALYSIS

Study purpose and objectives

The PICS-p study will address three objectives:

1. Determine the physical, cognitive, emotional and social health outcomes and trajectory of recovery in a population of children post-critical illness.
   Hypothesis: PICU survivors will experience a common set of physical, cognitive, emotional and social problems after critical illness and will demonstrate variable trajectories of recovery in the first 2 years post-critical illness.
2. Determine the baseline health, presenting problem and PICU factors associated with impaired physical, cognitive, emotional and social outcomes among PICU survivors.
   Hypothesis: Subgroups of PICU survivors will exhibit varying levels of recovery in their physical, cognitive, emotional and social health.
3. Determine the emotional and social health outcomes of parents and siblings of PICU survivors.
   Hypothesis: Families, including parents and siblings, will experience emotional and social health consequences of having a child or sibling who survived paediatric critical illness.

Study design

PICS-p is a prospective, multicentre, longitudinal cohort study that will enrol 750 children during their first PICU hospitalisation at 1 of 30 participating US sites to evaluate child and family outcomes in the 2 years following PICU discharge. The study cohort will be comprised of 500 case participants who experience ≥3 intensive care days that include at least one critical care therapy (box 1) and 250 control participants who experience a single night in the PICU with no intensive care therapies.

We will collect information about the child's baseline health status and PICU course. Child and family outcomes will then be measured at PICU discharge and at 2 weeks, 6 weeks and 3, 6, 12, 18 and 24 months after PICU discharge. After the 24-month follow-up period, a subset of parents will be selected for qualitative interviews regarding their experiences participating in this study, their perceptions about post-PICU recovery, as well as their preferences for post-PICU follow-up care. PICS-p study recruitment ran between July 2021 and November 2023. Data collection is anticipated to continue until January 2026.

Participants

Case/control participants

Inclusion criteria are purposely broad in scope (box 2). Exclusion criteria preclude enrolment of children not anticipated to survive 1 year after PICU hospitalisation and children in foster care and/or suspected of being maltreated. Control participants will be frequency matched to cases on a 2:1 case to control ratio based on age group (1–12 months, 13–23 months, 2–4 years, 5–7 years, 8–12 years and 13–15 years, as categorised in the Paediatric Quality of Life Inventory (PedsQL) Generic Core Scales[25] and Infant Scales[26]), sex and medical complexity (complex chronic disease, non-complex chronic disease, no chronic disease[27]). Each participating site will enrol approximately 20 case and 10 control participants over a 2-year enrolment period. To capture seasonal variation in PICU admission diagnoses, each site will screen and enrol consecutive eligible children up to a prespecified target on a quarterly basis. The Data Coordinating Center (DCC) will monitor case participant characteristics and

Box 1 Criteria for intensive care therapies

Examples of therapies and monitoring that are typically provided only in the paediatric intensive care unit. Examples are not subject to local practice patterns.

Multisystem
- ⇒ Extracorporeal life support (any type).

Respiratory
- ⇒ New tracheostomy.
- ⇒ Invasive mechanical ventilation.
- ⇒ Non-invasive mechanical ventilation (NIV): ≥48 hours of continuous positive airway pressure ≥5 cm H_2O or bilevel positive airway pressure.
  - ⇒ Paediatric acute respiratory distress syndrome or other acute lung disease: NIV plus PaO_2/FiO_2 ratio ≤300 or SpO_2/FiO_2 ratio ≤264 for at least 4 hours.
  - ⇒ Status asthmaticus: NIV plus ≥48 hours of continuous bronchodilator therapy (eg, albuterol, terbutaline or magnesium infusion).

Cardiovascular
- ⇒ Continuous infusion of titratable medications (eg, vasopressors/inotropes/antihypertensives/pulmonary vasodilators).
- ⇒ Cardioversion/defibrillation.
- ⇒ Cardiac pacing (any type).
- ⇒ Ventricular assist device.

Neurological
- ⇒ Continuous electroencephalogram monitoring for status epilepticus.
- ⇒ Intracranial pressure monitoring and treatment for intracranial hypertension.
- ⇒ Continuous vasopressin infusion.

Renal
- ⇒ Acute renal replacement therapies (eg, haemodialysis, continuous renal replacement therapy).

Haematological
- ⇒ Erythrocytapheresis/red blood cell exchange.
- ⇒ Plasmapheresis/plasma exchange.
- ⇒ Leukapheresis.

Hepatic
- ⇒ Extracorporeal hepatic support.

Surgical
- ⇒ Postoperative solid organ transplant.

Box 2 Post-intensive care syndrome in paediatrics inclusion and exclusion criteria

Eligibility criteria

Inclusion criteria
- ⇒ First intensive care unit (ICU) admission, including paediatric subspecialty ICU (eg, cardiac) and/or neonatal ICU.
- ⇒ Age ≥4 weeks (and ≥44 weeks corrected gestational age) and <16 years at PICU admission.
- ⇒ PICU length of stay:
  - ⇒ **Case participants:** ≥3 days (ie, covers ≥3 nights from 00:00 to 07:00) with at least one intensive care therapy for organ dysfunction (eg, invasive mechanical ventilation, vasopressors/inotropes; see box 1 for full list).
  - ⇒ **Control participants:** One overnight stay (ie, covers one 00:00 to 07:00 period) with no intensive care therapies for organ dysfunction.*
- ⇒ Anticipated discharge to home, directly or indirectly following stay in another facility (eg, rehabilitation).

Exclusion criteria
- ⇒ Does not live with at least one parent/legal guardian.
- ⇒ Life expectancy not anticipated to be more than 1 year (eg, active do-not-resuscitate order, palliative care team involvement for end-of-life symptom management).
- ⇒ Anticipated discharge into foster care, ward of the state or known or suspected child maltreatment.

PICU, paediatric intensive care unit.
*Postoperative patients extubated prior to parental presence in the PICU can be considered.

instruct sites to enrol a prespecified number and type (eg, specific age group or medical complexity) of control participants in the final two quarters.

Family participants

At least one eligible parent/legal guardian who is the child's primary care provider must be willing to participate. If two parents are willing, parents will self-select who will serve as the primary parent for the proxy-report surveys; the second parent may complete a separate set of self-report surveys independently. A subset of case and control parents who complete the 2-year data collection time point will be systematically selected for qualitative interviews. This will include parents of children of differing age and medical complexity. Interviews will continue until thematic saturation has been reached.

Up to two cognitively capable siblings (Paediatric Cerebral Performance Category (PCPC) <3)[28] aged 8–15 years who live with the patient at least 50% of the time and have not been previously hospitalised in an ICU will be invited to complete sibling surveys. If more than two siblings are eligible, the two siblings with the next birthdays after the patient's birthday, regardless of year, will be invited to participate.

Study sites and recruitment

Each participating site is a member of the Paediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network. Research staff at each site will screen their PICUs daily for eligible patients and enrol consecutive case and control participants each quarter. Parents/legal guardians will be approached for consent within 72 hours of PICU discharge. Children who have reached the age of assent (≥8 years), have not received sedation/pain medications for 72 hours and have PCPC <3 will be deemed cognitively capable and asked to provide assent. Adolescents who would reach their 18th birthday during the 2-year longitudinal follow-up (≥16 years at PICU admission) will not be enrolled. Eligible siblings will provide written assent while visiting the hospital or verbal assent by phone followed by an electronic assent if visits are not planned or, due to the COVID-19 pandemic, permitted.

Data collection and follow-up

Site research staff will collect demographic and clinical data through family interview prior to hospital discharge and data extraction from the electronic medical record.

These data include baseline medical history, developmental history, academic history, social influencers of health (ie, Child Opportunity Index[29]), household factors, health insurance type, presenting diagnosis, illness severity as measured by the Paediatric Risk of Mortality IV score[30] and hospital course factors (eg, duration of mechanical ventilation, PICU and hospital length of stay, organ dysfunction). Using provided contact information, parents will be sent electronic surveys to report their child's and family's status prior to PICU hospitalisation and a separate set of surveys to report their status at the time of PICU discharge. Assented patients and siblings will be sent surveys starting at 2 weeks post-PICU discharge.

After PICU discharge, data collection will be managed centrally by the Clinical Coordinating Center (CCC) and DCC. Surveys are primarily web-based using the electronic data capture platform REDCap (Research Electonic Data Capture) Cloud,[31] which distributes surveys through individual, secure email links. Prior to each follow-up time point, participants will receive an email to complete surveys with a completion window. Dependent on parent preference, email or text reminders will be sent or reminder phone calls will be made for surveys not completed within the time window. Participants will be instructed to report their status for the prior 7 days for first three sampling periods (2 weeks, 6 weeks and 3 months post-PICU discharge) and for the prior month for later sampling periods (6, 12, 18 and 24 months).

Participants with limited internet access or other extenuating circumstances will be given the opportunity to complete surveys by mail or telephone interview. If a child does not have a personal email address or is <13 years old, survey links will be sent to parents with instructions to share the link with their child. Each survey starts by asking the relationship of the respondent to the patient and the patient's (or sibling's) age. If a child is still hospitalised or is rehospitalised during the data collection period, data collection will be paused until the child returns home and will resume per the schedule based on the index PICU discharge date.

End-of-study interviews are anticipated to take at least 30 min and will be conducted by the study investigators or a trained study team member. At the beginning of the interview, the interviewer will obtain the parent's consent to record the interview. The interview guide was developed by the co-investigator team in consultation with the parent advisory group.

Spanish-speaking families will complete validated Spanish versions of all assessment instruments by mail or telephone interview with a Spanish-speaking research team member. If a Spanish-speaking family is selected for an end-of-study interview, the interview guide will be translated into Spanish and the interview will be completed with the assistance of a Spanish-speaking research team member.

Outcome measures

The primary outcome is HRQL for case and control participants as measured by the PedsQL V.4.0 Generic Core Scales[25] or Infant Scales[26] (table 1). The Generic Core Scales assess physical, emotional, social and school functioning in children 2–17 years. The Infant Scales assess physical functioning and symptoms and emotional, social and cognitive functioning in children <2 years. Both sets of instruments demonstrate validity and reliability,[32–34] have been widely used in PICU populations[35] and discriminate between healthy children and those with a wide range of acute and chronic health conditions.[36–38]

Secondary outcomes for case and control participants include measures of fatigue,[33] cognitive and functional status,[33 39–43] pain,[44 45] sleep disturbance,[46 47] growth and development,[48] emotional and behavioural health,[49 50] post-traumatic stress disorder (PTSD) symptoms[51 52] and hope[53] (table 1). Secondary outcomes for parents include family functioning,[54] resilience,[55] anxiety[56–58] depression,[58] sleep disturbance,[59] PTSD symptoms[60] and post-traumatic growth.[61] Secondary outcomes for siblings include quality of life,[25] participation in caregiving activities,[62] emotional and behavioural health[49 50] and hope.[53]

All outcomes will be measured at least three times over the 2-year follow-up period (table 2), except for resilience (measured at baseline and 18 months) and post-traumatic growth (measured at 12 months). See online supplemental file 1 for a full description of all survey measures. In addition, parent-completed surveys include questions about medical history after the index PICU discharge (eg, medical providers and prescribed medications) and missed school and work, as well as free-text fields asking about major life events occurring during the follow-up period (eg, move, divorce) and services and resources that are wanted but not being received.

The wording of the PedsQL V.4.0 Generic Core, Infant, Multidimensional Fatigue and Cognitive Functioning scales; PCPC and Paediatric Overall Performance Category; and Functional Status Scale (with owner permission) were modified in response to parent advisory group and participant feedback regarding the need for patient-centred and family-centred language. Text changes are noted in online supplemental files 1,2.

Analysis plan

The DCC will perform all statistical analyses for the PICS-p study. Descriptive statistics for demographic information, medical history, presenting illness, hospital course and all child, parent and sibling survey measures will be calculated, including means, SD, medians and IQRs 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.

To explore PICU survivors' health outcomes and trajectory of recovery, we will compare the outcome measures of case versus control participants using t-tests and linear regression adjusting for matching factors (age group, sex,

Table 1 Measures, participant burden and association with PICS-p framework

Measure	Age group (years)	Number of items	Time required (minutes)	PICS-p domain assessed*
Parent proxy-report for child				
PedsQL V.4.0 Generic Core or Infant Scales				P, C, E, S
Teen	13–17	23	<4	
Child	8–12	23	<4	
Young child	5–7	23	<4	
Toddler	2–4	21	<4	
Infant (13–24 months)	1–2	45	<10	
Infant (1–12 months)	0–1	36	<7	
PedsQL Multidimensional Fatigue Scale V.3.0		18	<4	P, C
Teen	13–17			
Child	8–12			
Young child	5–7			
Toddler	2–4			
PedsQL Cognitive Functioning Scale		6	<2	C
Teen	13–17			
Child	8–12			
Young child	5–7			
Toddler	2–4			
Survey of Well-being of Young Children – milestones only	0–5	10	2	P, C, S
Strengths and Difficulties Questionnaire (SDQ)		25	4	E, S
Teen/child	11–17			
Child/young child	4–10			
Toddler	2–4			
Young Child PTSD Screen – Revised PICU	3–17	6	2	E
Functional Status Scale	0–17	6	2–5	P
Paediatric Cerebral Performance Category	0–17	1	1	C
Paediatric Overall Performance Category	0–17	1	1	P
Parent proxy-report for family				
PedsQL Family Impact Module V.2.0	–	36	5	P, C, E, S
Parent self-report				
Connor-Davidson Resilience Scale-10	–	10	3	E, S
State-Trait Anxiety Inventory-40	–	40	10	E
State-Trait Anxiety Inventory-6	–	6	2	E
Patient Health Questionnaire-4	–	4	2	E
PROMIS Sleep Disturbance – Short Form 4a and Sleep-Related Impairment – Short Form 4a	–	8	3	P, E
PTSD Checklist for DSM-5	–	20	6	E
Post-traumatic Growth Inventory – Short Form	–	10	4	E
Patient self-report				
PedsQL V.4.0 Generic Core Scales		23	<4	P, C, E, S
Teen	13–17			
Child	8–12			
PedsQL Multidimensional Fatigue Scale V.3.0		18	<4	P, C
Teen	13–17			

Continued

Table 1 Continued

Measure	Age group (years)	Number of items	Time required (minutes)	PICS-p domain assessed*
Child	8–12			
PedsQL Cognitive Functioning Scale		6	<2	C
Teen	13–17			
Child	8–12			
PedsQL Paediatric Pain Questionnaire	8–17	2	1	P
PROMIS Paediatric Pain Interference – Short Form 8a (only if reporting pain in past week/month)	8–17	8	<2	P
PROMIS Paediatric Sleep Disturbance – Short Form 4a and Paediatric Sleep-Related Impairment – Short Form 4a	8–17	8	3	P, E
SDQ teen/child	11–17	25	4	E, S
Child PTSD Symptom Scale for DSM-5	8–17	27	10	E
Children's Hope Scale (CHS)	8–17	6	3	E
Sibling self-report				
PedsQL V.4.0 Generic Core Scales		23	<4	P, C, E, S
Teen	13–17			
Child	8–12			
Multidimensional Assessment of Caring Activities	8–17	18	2–4	S
SDQ teen/child	11–17	25	4	E, S
CHS	8–17	6	3	E

*P=physical health; C=cognitive health, E=emotional health, S=social health.
DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PedsQL, Pediatric Quality of Life Inventory; PICS-p, paediatric post-intensive care syndrome; PICU, paediatric intensive care unit; PROMIS, Patient-Reported Outcomes Measurement Information System; PTSD, post-traumatic stress disorder.

medical complexity). We will compare patients' outcomes to HRQL data from the general and chronically ill populations using t-tests. For consistency across age groups, parent proxy-report scores will be used in primary analyses. To explore response consistency, parent proxy-report and patient self-report will be compared in a separate analysis. For longitudinal data, we will assess correlations between time points using Pearson correlations and will use mixed linear regression models with random subject effects to analyse trajectories over time. We will use graphical analyses to display health outcome trajectories.

To identify factors associated with impaired health outcomes among PICU survivors, we will use Pearson correlations for continuous covariates and t-tests or analysis of variance for categorical covariates. We will use multiple linear or logistic regression modelling with variable selection techniques to adjust for baseline factors or confounding patient variables. We will compare patient versus sibling outcomes using paired t-tests, and we will compare patient, parent and sibling emotional and social health outcomes to published means using t-tests.

We will use mixed effects and generalised estimating equations models to explore whether adjustment for sex, race/ethnicity or site affects study inferences. If there are differences in baseline or PICU factors or early PedsQL measurements between participants with and without 1-year and 2-year data, multiple imputation methods and sensitivity analyses will be used to account for missing data due to attrition. Finally, classification and regression trees with recursive partitioning, principal component analysis, factor analysis and machine learning methods will be explored to help describe subgroups of patients with similar trajectories of outcome.

Audio data from end-of-study interviews will be transcribed verbatim, reviewed and pseudo-anonymised prior to formal thematic analysis.[63] NVivo V.12 software will facilitate qualitative data analysis. Codes will be collated and collapsed into subthemes and subsequent themes. The emerging findings will be periodically reviewed by the principal investigators and co-investigators to allow for the data analysis to be refined, enhancing the rigour.

Statistical power

Assuming 20% attrition, 2-year outcomes will be available for 400 case and 200 control participants. With these sample sizes, we will have >80% power to detect the minimum clinically significant difference of 4.5 points (0.283 SD)[36] for the primary outcome, PedsQL total score, between cases and controls. We will have 80% power to detect moderate differences (0.29 SD) between

Table 2 Schedule of survey completion

Measures	Baseline*/ PICU discharge	Post-PICU discharge†						
		Short-term			Long-term			
		2 weeks	6 weeks	3 months	6 months	12 months	18 months	24 months
Parents								
PedsQL V.4.0 Generic Core or Infant Scales	X/-	X	X	X	X	X	X	X
PedsQL Multidimensional Fatigue Scale V.3.0	X/-	X	X	X		X		
PedsQL Cognitive Functioning Scale					X		X	X
Survey of Well-being of Young Children	X/-			X			X	
Strengths and Difficulties Questionnaire (SDQ)	X/-				X	X		X
Young Child PTSD Screen – Revised PICU				X	X	X		X
Functional Status Scale	X/X			X		X		X
Paediatric Cerebral Performance Category	X/X			X		X		X
Paediatric Overall Performance Category	X/X			X		X		X
PedsQL Family Impact Module V.2.0		X		X		X	X	X
Connor-Davidson Resilience Scale-10	X/-						X	
State-Trait Anxiety Inventory-40	X/-							
State-Trait Anxiety Inventory-6				X		X		X
Patient Health Questionnaire-4	-/X		X		X		X	
PROMIS Sleep Disturbance – Short Form 4a and Sleep-Related Impairment – Short Form 4a	X/-	X		X		X		
PTSD Checklist for DSM-5				X	X	X		X
Post-traumatic Growth Inventory – Short Form						X		
Patients								
PedsQL V.4.0 Generic Core Scales		X	X	X	X	X	X	X
PedsQL Multidimensional Fatigue Scale V.3.0		X	X	X		X		
PedsQL Cognitive Functioning Scale					X		X	X
PedsQL Paediatric Pain Questionnaire	X/X‡	X	X	X	X	X		X
PROMIS Paediatric Pain Interference – Short Form 8a (only if reporting pain in past week/ month)	X/X‡	X	X	X	X	X		X
PROMIS Paediatric Sleep Disturbance – Short Form 4a and Paediatric Sleep-Related Impairment – Short Form 4a					X		X	X
SDQ					X	X		X

Continued

Table 2 Continued

Measures	Baseline*/ PICU discharge	Post-PICU discharge†						
		Short-term			Long-term			
		2 weeks	6 weeks	3 months	6 months	12 months	18 months	24 months
Child PTSD Symptom Scale for DSM-5				X	X	X		X
Children's Hope Scale (CHS)				X	X	X	X	X
Siblings								
PedsQL V.4.0 Generic Core Scales	X§/-		X	X	X	X	X	X
Multidimensional Assessment of Caring Activities	X§/-		X		X		X	
SDQ					X	X		X
CHS				X	X	X	X	X

*For the baseline/pre-PICU surveys, respondents are asked about the time period before the child's critical illness.
†Respondents asked about the prior 7 days for the short-term sampling periods and the prior one month for the long-term sampling periods.
‡Patients who self-report are asked about their pain before going to the hospital and at PICU discharge during their 2-week survey.
§Siblings are asked about the time period before their brother or sister's critical illness during their first survey, typically collected two weeks post-PICU discharge after assent is obtained.
DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PedsQL, Paediatric Quality of Life Inventory; PICU, paediatric intensive care unit; PROMIS, Patient-Reported Outcomes Measurement Information System; PTSD, post-traumatic stress disorder.

two case groups with different exposures or the case group with 200 matched siblings (0.29 SD). For multiple linear regression modelling on 400 cases using a two-sided 0.05-level test and assuming 5–10 covariates with an R^2 value of 0.10–0.30, we will have 80% power to detect a new predictor variable that improves R^2 by 0.017.

Patient and public involvement

A co-investigator team that collectively provides expertise in physical and functional health outcomes, child and family psychological evaluation, sibling support and biostatistics were integral in developing the study design, meets biannually with the study principal investigators to provide feedback and will assist with data interpretation. A parent advisory group comprised of parents who have had a child previously admitted to the PICU provided feedback on survey and interview guide development, will assist with ongoing problem-solving and will provide feedback on data interpretation at the end of the study.

Ethics and dissemination

Ethical review

Adhering to the National Institutes of Health (NIH) mandate for multisite research studies, the University of Pennsylvania (PENN) institutional review board (IRB) serves as the IRB of record or reviewing single IRB for this study (protocol #843844). PENN conducts the ethical review for all sites under a reliance agreement. This study has been externally peer-reviewed and awarded funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD; R01HD098269; MPIs Curley and Watson) and is coordinated by PENN and Seattle Children's Research Institute. The grant for this study was initially submitted for NICHD review on 31 May 2018 and resubmitted on 4 March 2019. Funding began on 1 July 2020. The study has been registered on ClinicalTrials.gov.

Quality assurance and control plans

Cohort retention procedures are based on investigator experience[14 17 64] and published strategies to maximise retention in longitudinal outcome studies.[65 66] Retention strategies include establishing rapport with families through contact at regular intervals of at least every 3 months by mail or email based on family preference (eg, quarterly family newsletters), centralised follow-up management by the CCC and flexibility in accommodating family schedules facilitated by the bicoastal research team to account for time zone differences. To maintain rapport, families receive family-oriented, study-branded tokens of appreciation (eg, fidget spinner, pop-its) at their 12-month study milestone. Participants are reimbursed for their time, and a public study website (afterpicu.com) is used to enhance study enthusiasm and provide families with PICS-p education, study information and procedures for securely updating contact information.

Follow-up surveys will be reviewed at regular intervals to monitor for potential mandated-reporting events (eg,

child maltreatment). Free-text fields are monitored for mention of harm to self or child.

Data management plan

Each site will maintain an enrolment log linking each patient to a unique study number. All contact information and clinical and survey data will be entered into the REDCap Cloud database developed and maintained by the DCC at Boston Children's Hospital. Only the study principal investigators, DCC and CCC teams have access to individually identifiable private information. The DCC regularly monitors the completeness, accuracy and consistency of the study database and produces regular reports on enrolment, data quality and completeness of participant follow-up. Qualitative data will be housed in a password-protected secure research drive accessible only to the principal investigators and their designee.

Dissemination

Children surviving critical illness are at risk for a broad spectrum of adverse sequelae including physical deconditioning, cognitive deficits, post-traumatic stress and impaired social development and family dynamics. The PICS-p conceptual framework describes this constellation of morbidities that may be uniquely experienced by children and families who survive paediatric critical illness.[7] The framework incorporates the influence of baseline health, socio-demographic characteristics, maturation and psychosocial development on a child's lifetime health trajectory and recognises the interdependence of the child and family. The PICS-p Longitudinal Cohort Study will test the applicability of this framework for critically ill children across the USA and comprehensively characterise post-PICU recovery to facilitate development of targeted interventions that prevent or mitigate adverse outcomes. Qualitative data on the post-PICU experience and parent preferences for post-PICU follow-up is separate but complementary to the quantitative survey data and will provide directions for future interventions.

The PICS-p study design includes several unique innovations. By comparing critically ill children undergoing ≥3 days of intensive care to control participants who spend a single night in the PICU without intensive care therapies, we will better understand the contribution of critical illness itself to adverse outcomes while also exploring whether there are common sequelae in all children or families who experience the PICU environment regardless of illness severity or exposure duration. If children or families experience emotional and social health consequences independent of the child's illness severity, as has been described,[10 67] efforts to reduce anxiety and trauma associated with a PICU stay may benefit all children and families exposed to the PICU environment. Conversely, if children exposed to multiple days of intensive care experience a common set of problems not experienced by control participants, this will support the concept of a syndrome of associated morbidities arising from the combined effects of severe illness and resulting therapies. Future mitigation approaches would focus on reducing the adverse impact of specific therapies and optimising recovery across subpopulations of the most critically ill children. In addition, measures of hope and resiliency will allow evaluation of family strengths affected by the PICU experience.

Although exclusion of children with prior ICU admissions will limit generalisability of study findings, it will allow us to explore the phenomenon of PICS-p from its onset and capture the development of chronic critical illness.[68] Chronic critical illness and PICS may share common pathophysiological mechanisms in adults,[69] but the relationship between new post-PICU morbidities and recurrent PICU admission has not been elucidated in children. The frequent follow-up assessment time points and 2-year study observation period provide opportunities to estimate the incidence of chronic critical illness development, explore how different domains of morbidity and recurrent PICU admission intersect and identify periods of vulnerability to high healthcare resource use during which children and families may benefit from increased support.

Outcome measures in the PICS-p Longitudinal Cohort Study were selected for alignment with the PICS-p conceptual model,[7] psychometric properties, ease of use, availability in Spanish, potential for child self-report and parent proxy-report, previous use in the PICU population[23] and consistency with the adult PICS literature.[70 71] Measures also align with the Paediatric Critical Care Core Outcome Set[72] and Core Outcome Measurement Set[73] developed by the PALISI and Collaborative Paediatric Critical Care Research networks with multidisciplinary stakeholder involvement from clinicians, researchers and families. Consistency between the domains and measures used in PICS-p and those recommended for use by the paediatric critical care community will facilitate comparison and integration of findings with future PICU outcomes research. As some instruments were designed for clinician use, text was revised when needed to improve inclusivity and patient-centredness and family-centredness of the chosen measures.

Measurement of outcomes across multiple time points will characterise trajectories of change for each phenomenon of interest and critical periods of vulnerability in each health domain to identify opportunities for focused interventions. We are implementing an evidence-based multimodal approach to optimise cohort retention and minimise loss to follow-up,[65 66 74–77] with an emphasis on longitudinal engagement with children and families. In addition to improving cohort retention, development of a culture of survivorship and engagement may have important implications for the health of PICU survivors and their families. Studies of childhood cancer survivors suggest that survivors who are engaged in follow-up care may have improved outcomes.[78]

Central to our ability to accurately assess trajectories of recovery is inclusion of recall estimates of children's baseline status prior to PICU admission. While most PICU

outcome studies compare follow-up scores to population means,[23] this approach does not capture clinically meaningful change for many children. The general paediatric populations on which instrument norms are based may have important differences from children experiencing critical illness who have a high prevalence of chronic health conditions[4 79 80] and baseline HRQL or functional status scores below population averages.[38] Comparison of post-PICU scores to population means may overestimate decline for participants whose baseline scores were low and underestimate decline for participants with baseline scores significantly above the population mean.[81] There is also a poorly characterised subset of children who experience improvement in health status following critical illness.[82–84] Although parent proxy-report and self-report of pre-PICU baseline may be affected by recall bias, anchoring assessment of change on pre-illness baseline will allow us to characterise the magnitude and direction of change for each measure and explore factors associated with both decline and improvement.

Finally, using the robust patient and clinical data collected in a geographically diverse sample recruited from 30 PICUs across the USA, we will characterise subgroups of children with unique risks for poor long-term outcomes. Identification of risk factors will stimulate development of targeted interventions focused on prehospital, in-hospital and post-discharge factors for high-risk patient groups. Identification of risk factors involving specific intensive care therapies or medications will inform interventional trials that avoid or minimise exposure to those factors to reduce patient morbidity. While enrolment is limited to families in the USA who speak English or Spanish, we will evaluate for differences in recruitment, retention and outcomes by race, ethnicity, language, social influencers of health and geography to understand how these factors may influence generalisability across populations. Data from PICS-p will allow for cross-national comparison to other ongoing studies in the field.[85–87]

Research is urgently needed to better understand morbidity among survivors of paediatric critical illness and identify strategies to optimise long-term outcomes.[88–90] The PICS-p Longitudinal Cohort Study will systematically and comprehensively determine the physical, cognitive, emotional and social health outcomes experienced following paediatric critical illness, identify periods of vulnerability in each health domain over 2 years following PICU discharge and inform interventions to reduce morbidity and optimise recovery among children surviving critical illness and their families.

Our dissemination strategy will be multifaceted to ensure findings are reported in a timely manner to clinicians, researchers and families. We will produce incremental publications (eg, 3-month, 6-month, 1-year, 2-year outcomes) as knowledge unfolds. We will target high-quality, peer-reviewed journals for publication. As manuscripts are published, they will be added to our public study website along with a brief plain language summary. Findings will be reported on ClinicalTrials.gov and presented at local, national and international meetings to increase understanding of the morbidities experienced by survivors of paediatric critical illness and their families. As per NIH policy, a de-identified data set and all data-related documentation necessary to use study data will be provided to the NICHD Data and Sharing Hub no later than 3 years after the final follow-up interview or 2 years after the primary paper has been published, whichever comes first.

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