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# Life After Pediatric Sepsis Evaluation (LAPSE)

**(LAPSE Study) CPCCRN Protocol Number 053**

Collaborative Pediatric Critical Care Research Network

*Eunice Kennedy Shriver* National Institute for Child Health

and Human Development (NICHD)

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Principal Investigator, Jerry J. Zimmerman, MD, PhD and the Collaborative Pediatric

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This protocol is CPCCRN Protocol Number 053, and has been authored by Jerry

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Lead Author:

Jerry J. Zimmerman, MD, PhD Seattle Children’s Hospital

Protocol Version: 1.07

Version Date: March 25, 2016

*I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Insti- tutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.*

Principal Investigator Name:

Principal Investigator Signature:

Date:

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**Abstract**

Sepsis, the complex host response to an invading pathogen, is among the most important clinical challenges in critically ill children. Severe sepsis in pediatrics is a major public health problem both in the U.S. where it accounts for *>* 4*,* 000 childhood deaths per year, as well as globally where the impact for children in the developing world is profound. Globally, it is estimated that nearly 29,000 children under the age of 5 die every day with four of the top 6 etiologies including infectious causes (diarrhea, malaria, neonatal infections and pneumonia). We have gleaned several key issues from clinical sepsis research to date: (1) outcome is related more so to the severity of host-pathogen interaction, than to pathogen identity, itself;

(2) the character of this interaction varies in a complex relationship between host developmental stage, host experience, and phase of illness; (3) outcome risk may be quantified as: (a) a function of sequential organ failure accrual; (b) acquisition of secondary nosocomial infections in terminal phases of illness; and (c) widespread energy failure secondary to cytopathic hypoxia; (4) there are a broad range of mechanistically-based sepsis sub-phenotypes, which reflect variation in the host- pathogen response (ranging from immune-paralysis to hyper-inflammation); (5) single-mechanism interventions fail in translation from specific animal models to un-characterized human sepsis populations.

As such, mounting evidence indicates that we may now have the potential to pair clinical management strategies to mechanistically-defined sepsis sub-phenotypes; this approach may improve ability to arrest progression of cascading organ failure and optimize outcomes. As noted, all prior clinical trials have combined different phenotypes, potentially lowering the signal to noise ratio and leading to failure to identify efficacious therapies. As children have increasingly survived the acute phase of illness, many ultimately die from progressive multiple organ dysfunction in the later phase and commonly, those that do survive are left with chronically diminished organ function and/or disability. Pediatric mortality from sepsis is relatively low (approximately 10%), and this has hampered the design and implementation of randomized therapeutic trials in sepsis. Moreover, patients and families expect return to the child’s baseline Health Related Quality of Life (HRQL) and functional status after surviving sepsis. However, in contrast to adult critical care, little is known about the long term outcomes following pediatric sepsis. This is an important gap in our knowledge because: (1) long term HRQL is a clinically meaningful but underutilized outcome measure for interventional clinical trials; (2) PICU practice and interventions may have profound influence on post-PICU HRQL; (3) recognition of risk for deterioration of HRQL may facilitate initiation of rehabilitation medicine interventions to facilitate optimal recovery; and (4) improving the quality of survival may be the most important goal of medicine.

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Iterative investigations by Wong and colleagues indicate that select serum pro- tein biomarkers predict risk for sepsis-associated mortality and/or complicated intensive care unit course for both adults and children. It is not known whether this biomarker model relates to sepsis-associated health related quality of life and functional status in survivors of severe pediatric sepsis.

This study will enroll infants and children with community acquired infection and severe sepsis. Subjects will be evaluated in detail to enable assessment of life quality as well as survival outcomes. We will quantify longitudinal HRQL and functional status (using the Pediatric Overall Performance Category [POPC] and Functional Status Scale [FSS]) following severe sepsis, and identify individual, environmental, and MODS characteristics that impact HRQL and functional status. Serum biomarkers will be measured to determine if Wong’s biomarker model also predicts magnitude of declination in sepsis-associated health related quality of life and functional status.

# Study Design Summary

The purposes of the LAPSE Study are: (1) quantify longitudinal HRQL and functional status following severe sepsis, compared to baseline; and (2) identify individual, envi- ronmental and MODS characteristics that impact HRQL and functional status; and (3) correlate biomarker profiles with HRQL and functional status. The protocol is summarized in Figure [1 on page 35](#_bookmark65).

Community acquired infection is operationally defined as suspected or documented infection diagnosed within 48 hours of admission to the hospital.

Severe sepsis is operationally defined as having two of four SIRS criteria (1 of the 2 must be fever, hypothermia, leukocytosis, neutropenia or 10% immature neutrophils), suspected or documented infection, cardiovascular organ dysfunction (requiring vasoac- tive inotropic infusion), and pulmonary organ dysfunction (requirement for invasive or non-invasive pressure support or mechanical ventilation).

Health Related Quality of Life (HRQL) is operationally defined as a combination of the Pediatric Quality of Life Inventory Generic Core Scales (PedsQL*T M* ), POPC score, FSS, and on-going co-morbid conditions.

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Informed consent will be obtained from the parents or legal guardians in order to obtain detailed baseline HRQL and functional status information, parental assessment of the child’s personality inventory, as well as for obtaining follow up HRQL and functional status data. Subjects who are capable of giving assent and who are alert and competent will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study for the collection of their personality self assessment and follow up self assessment of health related quality of life and function. If a subject declines to give assent, self assessment data will not be collected from the subject.

## Inclusion Criteria

Age 44 weeks gestation and *<* 18 years; AND Suspicion of sepsis or infection; AND

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* ≥

Systemic inflammatory response syndrome (SIRS) (at least 2 of 4 criteria); AND Community acquired infection or sepsis (diagnosis within 48 hours of hospital admission); AND

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Cardiovascular organ dysfunction (requiring vasoactive inotropic infusion); AND Pulmonary organ dysfunction (requirement for invasive or non-invasive pressure support or mechanical ventilation).

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At least one of the SIRS criteria must involve the patient’s white blood cell count (leukocytosis or neutropenia or 10% immature neutrophils) OR the patient’s body temperature (fever or hypothermia).

≥

## Exclusion Criteria

Thermal or electrical burn as primary reason for admission; OR

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Lack of commitment to aggressive intensive care as indicated by do not resuscitate orders or other limitations of care; OR

•

* + - Parents or guardians unable to speak English or Spanish; OR
    - Patient is ward of the state; OR
    - Patient is unable to participate in long term follow up; OR
    - Patient was previously enrolled in this study; OR
    - Patient was not able to be enrolled within 48 hours of PICU admission.

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## Anticipated Subject Accrual

Based on a CPCCRN pilot study, it is estimated that 125 patients per year will meet eligibility criteria for the study and survive their hospitalization. The LAPSE Study will enroll subjects for four years with a target accrual of 500 surviving subjects. Follow-up will continue during the fifth year of the study.

# Rationale and Background

Sepsis is the most common cause of childhood mortality worldwide, accounting for a pre-school child death every 4 seconds.[1](#_bookmark32)–[3](#_bookmark33) In the United States, 75,000 cases of pediatric severe sepsis hospitalization occur annually, with 6,800 deaths for a case fatality rate of 9%, and account for $4.8 billion in annual health expenditures.[4](#_bookmark34) This is an increased number of hospitalizations and slightly lower case fatality rate than previous reports.[5](#_bookmark35)–[7](#_bookmark36)

Although pediatric critical care medicine has clearly reduced pediatric critical illness mortality in general and sepsis mortality in particular,[8](#_bookmark37) children who survive an index case of sepsis are at increased risk for hospital readmission, frequently involving a second infection.[9](#_bookmark38) These findings suggest a substantial morbidity burden among children who survive sepsis. Indeed, children with pre-existing comorbidities represent an increasingly higher percentage of PICU admissions,[10](#_bookmark39) and comprise 34-49% of pediatric sepsis cases.[5](#_bookmark35), [7](#_bookmark36) Recent analysis of the database of the RESOLVE study,[11](#_bookmark40) the largest pediatric sepsis interventional trial conducted to date (*n* = 477), provides further evidence of long term morbidity. Adjunctive treatment with activated protein C provided no benefit in terms of faster resolution of composite organ dysfunction nor reduced mortality. However, the study population of sepsis survivors exhibited a very significant deterioration of gross functional status comparing baseline and 28 day measures of POPC scores.[12](#_bookmark41)

There is increasing recognition of the insensitivity of (short-term) mortality to evaluate the efficacy of a critical care intervention.[13](#_bookmark42) It has been noted that “Non-mortal measures of benefit assume particular importance for populations such as children, whose mortality risk is low, or who have significant rates of co-morbidities that independently limit survival. Composite measures that integrate morbidity and mortality effects may provide the most meaningful information about therapeutic efficacy”.[14](#_bookmark43)

In both adult[15](#_bookmark44) and pediatric[5](#_bookmark35), [7](#_bookmark36), [16](#_bookmark45)–[18](#_bookmark46)sepsis, number and intensity of organ dysfunc- tions identify risk for death. Death from sepsis nearly always involves MODS.[15](#_bookmark44) In a cross-sectional cohort follow-up study of 322 adults 2-7 years after surviving trauma,

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trauma-related MODS was associated with increased mortality after hospital discharge and a 3.9 times higher odds of requiring long term personal assistance for activities of daily living compared to patients not developing MODS.[19](#_bookmark47)Among a cohort of 1339 adults admitted for community acquired pneumonia, acute organ dysfunction occurred in 48%.[20](#_bookmark48) Surviving patients were assessed at 90 days. Acute organ dysfunction was associated with increased late mortality (*p <* 0*.*00001), as well as impaired HRQL (*p* = 0*.*006) and FS (*p* = 0*.*009). Importantly, after adjusting for baseline HRQL, no association was detected between organ dysfunction and late mortality (*p* = 0*.*47), and the evidence of association between organ dysfunction and sustained impaired HRQL was weak (*p* = 0*.*14). “The early morbidity of sepsis is reflected in deranged organ function and the need for ICU supportive care. . . After the acute illness resolves, the patient may still require a lengthy hospital stay and subsequent rehabilitation, with the attendant physical, emotional, and financial bur- dens; long term morbidity is reflected in reduced HRQL.”[14](#_bookmark43) These data are from studies of adult patients; it is poorly understood how MODS affects long term HRQL/FS in children.

In summary, future interventional trials in pediatric sepsis cannot be powered solely on mortality, and understanding the impact of severe sepsis on HRQL and FS of survivors may provide more suitable and feasible endpoints for these future studies. Patterns of multiple organ system failure may permit more efficacious stratification of subjects at the onset of an interventional trial, as different patterns of MODS may reflect fundamentally different sepsis phenotypes that should be approached with very different clinical strategies. The LAPSE Study will describe the morbidity generated among children surviving severe sepsis utilizing validated tools to measure Health Related Quality of Life and functional status. LAPSE will also examine how key individual, environmental, and organ failure characteristics affect these clinically meaningful outcomes.

# Study Endpoints and Hypotheses

The LAPSE Study will enable the following analyses:

*Characteristics of Severe Sepsis:*

Clinical, laboratory and microbiologic characteristics of subjects with community acquired infection who develop severe sepsis.

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Assessment of severity and duration of specific organ failures that directly affect systemic oxygen delivery (cardiovascular, pulmonary, hematologic, and metabolic) in children with severe sepsis.

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*Health Related Quality of Life and Functional Status in Severe Sepsis Survivors:*

Quantification of altered HRQL (PedsQL*T M* ) from baseline in survivors of severe sepsis at 7 and 28 days, and 3, 6, and 12 months following admission to the PICU for the sepsis event; quantification of altered functional status (FSS, PCPC/POPC) from baseline in survivors of severe sepsis at 7 and at 28 days or hospital discharge, whichever occurs first.

•

Exploratory correlation of HRQL deterioration and recovery toward baseline in survivors of severe sepsis with duration and severity of organs affected by MODS during the course of severe sepsis in the PICU.

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Exploratory correlation of HRQL deterioration and recovery toward baseline in survivors of severe sepsis with the child’s comorbid conditions and personality traits, and environmental characteristics (including socioeconomic factors, family dynamics and parental stress).

•

We hypothesize that we will observe significant variation of HRQL and functional status following survival of severe sepsis, enabling development of suitable composite outcome measures for future interventional trials for pediatric sepsis. We further hypothesize that deterioration of HRQL and functional status following survival of severe sepsis will correlate with (1) the intensity and duration of specific organ failures that adversely affect systemic oxygen delivery and consumption during the acute illness; and (2) characteristics of the individual (chronic comorbid conditions, personality traits) and environment (socioeconomic factors, family dynamics and parental stress). Finally, we hypothesize that the biomarker profile identified in previous studies by Wong, which has already been shown to predict mortality[21](#_bookmark49), [22](#_bookmark50) will be associated with increased risk of poor long term outcome and impaired HRQL in survivors of pediatric sepsis. Such an association would form a valuable stratification strategy in future interventional trials of pediatric sepsis.[23](#_bookmark51)

# Data Collection and Procedures

Data collection will include the age, gender, race, ethnicity, SIRS variables, daily mon- itoring for organ system failure, dates of admission and discharge, death, length of hospital and PICU stay, and status at PICU and hospital discharge. These data ele- ments form Dataset 1. Data collection will also include daily clinical and laboratory variables, treatment information, culture results, and interventions during the PICU hospitalization (Dataset 2). Individual and environmental modifiers include a personality inventory (to assess child personality traits, parent assessment), socioeconomic data, the Family Assessment Device, and the Brief Symptom Inventory (Dataset 3). Baseline

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HRQL (PedsQL*T M* ) will be assessed and this assessment repeated at 7 and at 28 days. Baseline functional status (FSS, PCPC/POPC) will be assessed and these repeated at 7 days and at 28 days or hospital discharge, whichever occurs first. HRQL follow up evaluations (PedsQL*T M* ) will also be obtained at 3, 6 and 12 months following PICU admission for the sepsis event by secure Internet, mail, telephone, or clinical visit, as appropriate and financially possible (Dataset 5). The POPC score, PCPC score, and FSS will not be assessed post hospitalization. Redundant contact information for the subject and family will be collected during hospitalization to facilitate follow-up; this information will be retained at each clinical site and will be sent to the Seattle Children’s Research Institute Outcomes Assessment Program. Contact data will not be entered into the study database maintained at the Data Coordinating Center at the University of Utah.

Date of PICU admission is study day zero. For subjects who are identified after the day of PICU admission but within 48 hours of PICU admission, daily data for study day zero (the day of PICU admission) should also be completed. For example, if a child is admitted to PICU at 3:00 PM on Sunday with suspected community acquired infection and SIRS, but does not have cardiovascular failure or pulmonary failure until 3:00 AM on Monday, then the child became eligible on Monday. Monday is study day one. Sunday, the day of PICU admission, is study day zero. Daily data collection should be completed for both days (Day 0 and Day 1).

Each of the five conceptual datasets are described below. Note that the specific questions and choice sets that are described in the following sections may not represent the final data collection forms built in the electronic data capture system. If substantively new data elements are added to the study, this protocol will be amended and submitted to the Institutional Review Board (IRB) for amendment approval.

## Study Datasets

### Dataset 1. Enrollment and Organ System Monitoring

*Demographic Summary Form:*

* + - * Birthdate
      * Gender
      * Race
      * Ethnicity

*Hospitalization Summary Form:*

* + - * Date and time of hospital admission

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* Date and time of PICU admission
* Date and time of hospital discharge
* Date and time of PICU discharge
* Vital status at PICU and hospital discharge (alive or dead)
* Date and time of death (if applicable)
* Autopsy obtained (Y/N/NA)
* If autopsy obtained, upload full report

*Diagnostic Codes:*

ICD9, and when applicable, ICD10 diagnostic codes (electronic batch submission). This may be accomplished from hospital information systems or, if available, may be obtained from each hospital’s access to the Pediatric Hospital information System (PHIS). The majority, but not all, of CPCCRN clinical centers participate in PHIS and have access to their PHIS database.

*Eligibility Form:*

Date of study eligibility

•

SIRS criteria met at time of eligibility:

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* Hypothermia (*<* 36 *◦*C) or fever (*>* 38*.*5 *◦*C);
* Leukocytosis (*>* 12*,* 000) or neutropenia (*<* 4*,* 000) or *>* 10% immature neu- trophils;
* Heart rate *>* 90th percentile for age in absence of stimulation;
* Respiratory rate *>* 90th percentile for age OR hyperventilation to *PaCO*2 *<*32 torr OR requirement for mechanical ventilation unrelated to drug administra- tion.

Nature of infection (documented infection, suspected infection) Type of organism (documented or suspected):

•

•

* Bacterial
* Fungal
* Viral
* Protozoal

### Dataset 2. Acute PICU Hospitalization Data

Date of PICU admission is study day zero. As described previously, if a child becomes eligible for enrollment the day after PICU admission, the following daily forms must be filled out for the day of admission as well as the day of enrollment. The data forms should

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be completed until PICU discharge or study day 28, whichever occurs first.

*Baseline Clinical Data Form:*

Weight (kg) Height (cm)

•

•

Immunocompromised (Y/N)

•

If immunocompromised, provide reason:

* Congenital immunodeficiency (Y/N)
* Bone marrow or stem cell transplantation (Y/N)
* Graft versus host disease (Y/N/NA)
* Solid organ transplantation (Y/N)
* Malnutrition, severe (Y/N)
* Malignancy (Y/N)
* Chemotherapy or radiotherapy within last 3 months (Y/N)
* Human immunodeficiency virus (Y/N)
* Rheumatologic disease (Y/N)
* Neutropenia (ANC *<*1000) (Y/N)
* Sickle Cell Disease (Y/N)
* Systemic steroid use, chronic or acute (Y/N)
* Other immunosuppression description (free text)

*PRISM III Form:*

* + - * Total PRISM Score for PICU admission (calculated by DCC statisticians)
      * PRISM Score components

*Single Daily Laboratory Data Form:*

* + - * Lowest absolute lymphocyte count
      * Lowest absolute neutrophil count
      * Lowest hemoglobin
      * Highest INR
      * Highest creatinine
      * Highest BUN
      * Highest total bilirubin
      * Highest alanine transaminase (ALT)
      * Highest lactate dehydrogenase (LDH)
      * Highest triglycerides

*Daily Vital Measurements Form (closest to 8 AM and 8 PM):*

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* Systolic Blood Pressure
* Diastolic Blood Pressure
* Mean Arterial Pressure
* Central Venous Pressure
* SpO2
* Central Venous Oxygen Saturation

*All Value Daily Laboratory Form:*

* Platelet count
* Fibrinogen
* Fibrin degradation products titer
* d-dimer
* Prothrombin time (PT)
* Arterial lactate concentration
* Amylase
* Lipase
* CRP
* Ferritin
* Free hemoglobin
* sCD25
* NK activity
* Bone marrow biopsy results (upload report)
* Genotyping for perforin mutations

*Respiratory Parameter Data Form (closest to 8 AM and 8 PM, simultaneous values):*

* Ventilator mode
* Fraction of inspired oxygen (0.21 to 1.00)
* Arterial PO2
* Arterial PCO2
* End Tidal CO2
* PEEP (cm H2O)
* PIP (cm H2O)
* MAP (cm H2O) for oxygenation indices
* Delivered (exhaled) tidal volume (ml) for dynamic compliance
* Nitric oxide (Y/N)

*Daily PICU Interventions / Clinical Findings Form:*

* Study day date

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* + Study day number
  + Infectious nidus removed by this study day (Y/N/NA/Unknown)
  + Inflammation source effectively removed by this study day (Y/N/NA/Unknown)
  + Mechanical ventilation (Y/N)
  + High frequency ventilation (oscillator or jet) (Y/N)
  + Extracorporeal support (ECMO or VAD) (Y/N)
  + Renal replacement therapy (hemofiltration or dialysis) (Y/N)
  + Cardiopulmonary arrest; chest compressions (Y/N)
  + Treatment for increased intracranial pressure (Y/N)
  + Immune suppressant tapered by 50%? (Y/N)
  + Plasma exchange therapy (Y/N)
  + Indwelling arterial catheter (Y/N)
  + Indwelling urinary catheter (Y/N)
  + Indwelling central venous catheter (Y/N)
  + Endotracheal tube in place (Y/N)
  + Tracheostomy in place (Y/N)
  + Indwelling central venous catheter (Y/N)
  + Splenomegaly (Y/N)
  + Neuromuscular blocker (Y/N)
  + Parenteral nutrition (Y/N)

*Daily PICU Fluid Parameters:*

* + Study day date
  + Study day number
  + Total 24 hour urine output (ml)
  + Red blood cell transfusion total volume (ml) (enter zero if none)
  + Platelet transfusion total volume (ml) (enter zero if none)
  + Plasma transfusion total volume (ml) (enter zero if none)

*Daily PELOD2 Scoring Form:*

* + PELOD2 component values
  + PELOD2 score (calculated by DCC Statisticians)

*Microbiology Results Log Form:*

Date microbiology specimen obtained Sample site:

•

•

* + - Abscess
    - Blood

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* Bronchial brush
* Bronchoalveolar lavage
* Nasopharyngeal
* Pleural fluid
* Peritoneal fluid
* Skin
* Spinal fluid
* Sputum
* Stool/Rectal
* Surgical Site
* Urine
* Vascular catheter
* Wound (non-surgical)
* Other (but no specify) Test type:

•

* Culture
* PCR
* Other
* Test result (negative, positive, contaminant)
* If test result positive OR contaminant, upload test report, including sensitivities

*Antimicrobial Administration Log Form:*

This form will record systemic antibiotic, antifungal or antiviral administration only.

Topical agents to skin, eye, wounds, etc. should not be recorded.

* Name of antimicrobial
* Start date
* Stop date

*Immune Medication Administration Log Form:*

This form will record steroids, other immunosuppressive drugs, chemotherapy, and immune-modulating drugs (systemic corticosteroids, hydrocortisone, methylprednisolone, dexamethasone, Primary HLH directed chemotherapy, G-CSF, GM-CSF, IVIG, etoposide, Rituximab, Tocilizumab, Infliximab, Anakinra, Dacilizumab, Basilixumab, etc.).

* Name of drug
* Start date
* Stop date

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* + Total 24 hour dose (applies to systemic corticosteroid medications only)

*Vasoactive Inotropic Score Form:*

This form will record intravenous continuously infused vasoactive drugs being received by a patient at 8 AM and 8 PM each day.

Study day date Study day number

•

•

Time (8 AM or 8 PM)

•

Subject receiving vasoactive drips? (Y/N) If subject is receiving vasoactive drips:

•

* Name of drug:

Dopamine Dobutamine Nitroprusside Milrinone Epinephrine Norepinephrine Phenylephrine Vasopressin

∗

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* Rate of infusion

*Daily CNS Screening:*

* + Anisocoria or absence of pupillary response (Y/N)
  + Pathologic breathing pattern (Y/N)
  + Stereotypic posturing or flaccid posture (Y/N)
  + Seizure activity and/or abormal EEG (Y/N)
  + New anoxic-ischemic injury on CT/MRI imaging (Y/N)
  + Neurologic injury suspected by care provider (Y/N)
  + Autonomic storming (Y/N)

The items are assessed for the entire study day and need not occur at the same time.

### Dataset 3. Baseline Individual and Environmental Modifier Data

The individual characteristics include the child’s comorbid conditions, which will be derived from ICD9 data that are already part of Dataset 1, and the child’s personality traits.

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The environmental characteristics include socioeconomic data, assessment of family dynamics using the Family Assessment Device (FAD), and parental stress (assessed with the Brief Symptom Inventory).

### Dataset 4. Baseline Quality of Life and Functional Status Data

These data will be obtained from parents or other usual caregivers and should assess the subject’s baseline health related quality of life and baseline socioeconomic status prior to admission to the hospital. Individuals providing proxy reports for this baseline data should be instructed to record scores based on the child’s typical or average status during the one month prior to hospitalization for the severe sepsis event. When appropriate clinically, the subject also will provide a self assessment of baseline health related quality of life. Typically this self-report would occur near the time of PICU discharge when the subject is not influenced by analgesics or anxiolytics or the presence of an endotracheal tube.

Research coordinators should assist but not influence collection of baseline HRQL data from parents, explaining the survey instruments so that parents are familiar with the tools.

Pediatric Quality of Life Inventory Generic Core Scales (Parent and Child reports) (PedsQL*T M* )

•

Functional Status Score POPC

•

•

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•

Baseline co-morbid conditions (based on ICD9 or ICD10 data) Chronic Medical Devices (free text)

•

•

Chronic Medications (free text) Residence status

•

•

* Residing at home with parents/guardian, not requiring rehabilitation program
* Residing at home with parents/guardian with outpatient rehabilitation program
* Residing at home with skilled nursing care
* Residing with foster care
* In an inpatient rehabilitation facility
* In chronic care or skilled nursing facility
* In acute care hospital, non-ICU
* In ICU

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**–** Other (free text)

Number of people living in home

•

Number of children under 18 living in home

•

Presence in home of any other child with chronic condition requiring chronic medical attention (Y/N)

•

Smoking in the home

•

* None
* Mother
* Father
* Others (no specify needed) Socioeconomic data:

•

* Health Insurance Status
* Primary caregiver
* Primary caregiver age category
* Primary caregiver marital status
* Primary caregiver educational level
* Annual household income

### Dataset 5. Followup Quality of Life and Functional Status Data

Follow-up HRQL (PedsQL*T M* ) assessments will be obtained from parents at 7 and 28 days and at 3, 6, and 12 months following PICU admission for the sepsis event. Follow-up functional status (FSS, PCPC/POPC) assessments will be obtained from hospital care providers or direct assessment at 7 and at 28 days or hospital discharge, whichever occurs first, following PICU admission for the sepsis event. When possible, the subject also will provide a self assessment of health related quality of life. Assessments after hospital discharge will be obtained by secure Internet, mail, or telephone, as appropriate and financially possible. Assessments following discharge from the hospital will be obtained by research staff at Seattle Children’s Research Institute Outcomes Assessment Program.

The assessments prior to hospital discharge may be estimated by the research coordi- nators or obtained from the clinical caregivers or parents, as deemed appropriate.

Pediatric Quality of Life Inventory Generic Core Scales (Parent and Child reports) (PedsQL*T M* )

•

* + - * Functional Status Score
      * POPC
      * PCPC

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Current medications (free text)

•

Current medical assist devices (free text) Hospitalizations since previous assessment (number)

•

•

Emergency room visits since previous assessment (number) Medical office visits since previous assessment (number)

•

•

Telephone calls to physician office since previous assessment (number)

•

New medical issues since previous assessment (parent assessment, free text) Vital status

•

•

* Alive
* Deceased

Residence status (if alive)

•

* Residing at home with parents/guardian, not requiring rehabilitation program
* Residing at home with parents/guardian with outpatient rehabilitation program
* Residing at home with skilled nursing care
* Residing with foster care
* In an inpatient rehabilitation facility
* In chronic care or skilled nursing facility
* In acute care hospital, non-ICU
* In ICU
* Other (free text)

Number of people living in home

•

Number of children under 18 living in home

•

Presence in home of any other child with chronic condition requiring chronic medical attention (Y/N)

•

Smoking in the home

•

* None
* Mother
* Father
* Others (no specify needed)

The individual characteristics include the child’s comorbid conditions, which will be derived from ICD9 data if there have been subsequent hospitalizations (otherwise, comorbid conditions will be based on a parent assessment), and the child’s personality traits. The latter will be assessed using a personality inventory (for subjects *>* 6 years of age) for self assessment by the child, or for parental assessment by the parents.

The environmental characteristics include assessment of family dynamics using the Family Assessment Device (FAD), and parental stress (assessed with the Brief Symptom

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Inventory).

At the time of the baseline survey and the 12 month follow-up, participating families will be asked if they would like to be contacted for potential future studies related to LAPSE. Interested families will document their consent to be contacted by checking a box on the DatStat Survey form. Participating families who already completed the LAPSE study but did not have the opportunity to be contacted for potential future studies will be mailed a letter inquiring if they would be interested in being contacted for potential future studies related to LAPSE. The letter will contain a pre-addressed postcard indicating an opt-out preference that can be mailed to the Seattle Research Institute if the participating family prefers not to be contacted for future studies. Letters will be mailed a minimum of six weeks prior to contacting families regarding other research studies.

## Blood Sampling and Processing

Unused serum samples will be obtained from the performance site clinical laboratories during the first 24 hours of PICU stay, and if possible, on the third day of PICU stay. Each sample must contain 50*µ*L of serum. If a sample cannot be obtained on day 1, no sample will be obtained on day 3.

≥

Samples will be stored in original clinical blood tubes or individually transferred to small storage tubes, labeled with time and date of collection as well the unique LAPSE subject identification number, and maintained refrigerated at 4*◦*C prior to shipping to the central laboratory. Paired serum samples (reflecting PICU day 1 and 3) will be transported cold with freezer pack by express delivery service to the central laboratory in Cincinnati.

The plasma biomarkers were selected objectively, based on extensive, discovery ori- ented transcriptomic studies.[24](#_bookmark52) The biomarkers include: C-C chemokine ligand 3 (CCL3), interleukin 8 (IL8), heat shock protein 70 kDa 1B (HSPA1B), granzyme B (GZMB), and matrix metallopeptidase 8 (MMP8).

The analyses of the biomarker samples in Cincinnati will consume the samples, and storage of samples for subsequent studies is not planned. Residual sample material will be discarded after biomarker analyses are completed.

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## Study Workflow

All PICU patients who meet study inclusion criteria should be screened and the parents of eligible subjects (who have no exclusion criteria) should be approached to obtain informed consent. Information concerning baseline status should be obtained as soon as it is feasible after enrollment in order to reduce biased recall of the child’s baseline status.

For subjects who do not survive hospitalization, contact information should not be sent to the Seattle Children’s Research Institute Outcomes Assessment Program. Contact information for surviving subjects should be sent to Seattle, and a copy retained at the clinical center. One week prior to scheduled follow up assessments, the clinical center staff should contact the family to find out if the child remains alive (if the child has died, then the date of death should be obtained). If the child is alive, the family contact information should be confirmed and the family should be told to expect a contact from research staff at the Seattle Children’s Research Institute Outcomes Assessment Program. If the contact information changes, the clinical center should send the updated contact information to Seattle to facilitate the follow up assessment.

# Data Analysis

*Characteristics of Severe Sepsis:*

Clinical, laboratory and microbiologic characteristics of subjects with community acquired infection who develop severe sepsis.

•

Assessment of severity and duration of specific organ failures that directly affect systemic oxygen delivery (cardiovascular, pulmonary, hematologic, and metabolic) in children with severe sepsis.

•

Descriptive statistics will be employed to characterize the study cohort in terms of demographics, infection, and illness severity (PRISM[25](#_bookmark53)) at enrollment. Severity of cardio- vascular organ dysfunction will be assessed using the vasoactive-inotropic score at 8 AM and 8 PM each day, as well as serial lactate measurements. Pulmonary organ dysfunction will be assessed by examining the oxygen saturation index, PaO2/FiO2, and dynamic compliance closest to 8 AM and 8 PM each day. Hematologic organ dysfunction will be assessed by the hemoglobin and the DIC score. For several of these scores, an area under the curve (AUC) will be constructed to enable correlation with long-term patient outcomes.

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*Health Related Quality of Life and Functional Status in Severe Sepsis Survivors:*

Quantification of altered HRQL (PedsQL*T M* ) from baseline will be assessed in survivors of severe sepsis at 7 and 28 days, and at 3, 6, and 12 months following admission to the PICU for the sepsis event. Quantification of altered functional status (FSS, PCPC/POPC) from baseline will be assessed in survivors of severe sepsis at 7 and 28 days or hospital discharge, whichever occurs first, following admission to the PICU for the sepsis event.

•

The primary measure of HRQL will be PedsQL*T M* GCS Version 4.0 per parent/guardian proxy report.[26](#_bookmark54) It has been noted that typically parents’ perceptions of their children’s HRQL is what drives health care use.[27](#_bookmark55), [28](#_bookmark56)

Coma, vegetative state or death will be scored as 0/100 for the PedsQL*T M* GCS score. Typically a very low % of missing item responses is noted with PedsQL*T M* GCS. However, percent of missing items will be recorded as a measure of instrument feasibility in this setting.[29](#_bookmark57) To account for any missing data, scaled scores will be computed as the sum of items divided by the number of items answered. If *>* 50% of the items in a particular scale are missing, the scaled score will not be computed for that subject.[30](#_bookmark58)

HRQL deterioration will be defined as a decrease from baseline *>* 10% in PedsQL*T M* GCS 28 days following PICU admission for the sepsis event. Based on previous work[9](#_bookmark38), [12](#_bookmark41) we predict that this will occur in 30 40% of subjects. Magnitude of deterioration will be defined as the absolute change in PedsQL*T M* GCS comparing baseline and 28 day evaluations. A change of 4.5 in PedsQL*T M* is considered a minimally clinically important difference among previously healthy children.[31](#_bookmark59) Scores one standard deviation below the healthy population mean score (65.4% per parent proxy-report) indicate children at risk status for impaired HRQL.[32](#_bookmark60)

≈ −

Serial PedsQL*T M* scores from severe sepsis subjects will be compared to pediatric normative data available for this instrument. To complement the assessment of HRQL with the PedsQL*T M* , we will also measure the gross and granular functional status of children surviving severe sepsis using the POPC Scale[33](#_bookmark61)–[35](#_bookmark62)and the FSS.[36](#_bookmark63)

PedsQL*T M* measures will be summarized at baseline, 7 and 28 days and 3, 6 and 12 months following PICU admission for the sepsis event.

* Exploratory correlation of HRQL deterioration and recovery toward baseline in

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survivors of severe sepsis with duration and severity of organs affected by MODS during the course of severe sepsis in the PICU.

The AUC for each organ dysfunction score will be correlated with the magnitude of HRQL deterioration measured 28 days after PICU admission using PedsQL*T M* , POPC, and FSS. The multivariable models will be adjusted for other patient characteristics and the length of hospitalization. Severity of organ dysfunction will also be correlated with the subsequent trajectory of recovery toward baseline over the subsequent evaluations.

Exploratory correlation of HRQL deterioration and recovery toward baseline in survivors of severe sepsis with the child’s comorbid conditions and personality traits, and environmental characteristics (including socioeconomic factors, family dynamics and parental stress).

•

Descriptive methods will be used to analyze correlation of non-medical factors with the magnitude of HRQL deterioration measured 28 days after PICU admission, and the subsequent trajectory of recovery toward baseline over the subsequent evaluations.

Descriptive statistics and regression will be used to test for associations between biomarker levels, and the trajectory of deterioration or improvement of HRQL and func- tional outcome.

# Data Management

The investigators and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. Study worksheets are to be completed in a neat, legible manner to ensure accurate interpretation of data. Any corrections or changes on the worksheets when made, the original entry should be crossed out using a single line, and must be dated and initialed by the individual making the change. The original entry will not be erased or overwritten.

## Electronic Data Capture Systems

Data from this study will be entered into an electronic data capture (EDC) system used by the Data Coordinating Center (DCC). Follow up data after hospital discharge will be obtained by research staff at the Seattle Children’s Research Institute Outcomes Assessment Program. The security of these two computer systems is described below.

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## Data Security (Utah)

The DCC is located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art data center infrastructure with a dedicated secure server facility with racks, inline cooling, uninterruptible power supply, high speed networking, security cameras, firewall protection, and 24/7 systems and security monitoring. The server facility is locked separately from the remainder of the DCC and access to the building is monitored by security personnel year round. The DCC coordinates its network infrastructure and security with the Health Sciences Campus (HSC) Information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intru- sion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. The EDC system, eRoom*T M* (Web-based collaborative workspace), and other web applications use the SSL protocol to transmit data securely over the Internet. Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against DCC servers, and DCC IT staff are notified of intrusion alerts.

Servers are backed up daily through a dedicated backup server and internal high speed network. Incremental backups occur hourly and nightly. Full system backups occur nightly and weekly with off-site rotations. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

## Survey Data Collection (Seattle)

Seattle Children’s Research Institute Outcomes Assessment Program will be responsible for post-hospital discharge follow-up on survivors in this study. Participants will complete followup surveys through DatStat*T M* , a secure web based survey program. DatStat*T M* maintains extremely stringent levels of encryption and data storage. The technology platform including servers, database, and web presences that employ multiple forms of security features to protect data and the participants involved in data collection efforts. All DatStat*T M* servers used for data collection are highly fault-tolerant and are equipped with redundant, hot-pluggable power supplies, redundant network interfaces, and RAID

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1/5 hot-pluggable disk storage. All primary servers are plugged into a monitored uninter- ruptible power supply (UPS) offering a minimum of 30 minutes of battery power in the event of a power outage. At least one additional server is available at all times to handle the off-chance of a major server crash.

DatStat*T M* secure servers are registered with site certificates provided by VeriSign Internet Trust Services that provides for advanced encryption over the wire. As users move through the data entry forms, the responses are encrypted while in-transit between the browser and the DatStat*T M* server using SSL (Secure Sockets Layer) and 128-bit Public Key Encryption. DatStat*T M* servers are stored in a locked, well-ventilated room in locked server cabinet/racks. The server room is in a building with 24/7 alarm security.

Protection of servers from remote attacks is accomplished with a dedicated hardware Watchguard firewall with auditing enabled at the recommended settings. Watchguard LiveSecurity keeps DatStat*T M* IT staff advised of all known security alerts. The firewall ensures that all traffic is closely monitored and suspicious packets blocked from access to the production systems. Security patches are applied to DatStat*T M* servers on a timely and ongoing basis. Logs are created by the web servers to increase accountability and are essential in investigating incidents after the fact. The following are logged: failed and successful logins, attempts to access files/directories without authority, successful and failed attempts to access sensitive data.

DatStat*T M* SQL Server database backups are conducted by DatStat*T M* on a daily basis. Backups are encrypted and streamed to a secure offsite location. Backups are encrypted using 256-bit AES encryption. Physical access to servers and data backup is also restricted to a minimal number of DatStat*T M* IT professionals. Such access is provided only with strong passwords that regularly expire. Access to data stored in the server is available only to designated DatStat*T M* users who log in with specified usernames and passwords.

On a regular basis the DCC will obtain survey data from the DatStat*T M* system to merge with the other study data.

## Protection of Confidentiality

The investigators and staff of the DCC are fully committed to the security and confiden- tiality of all data collected for CPCCRN studies. All DCC personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the

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center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

The coordinators, reviewers and investigators involved with this study will be required to sign agreements from the DCC that relate to maintenance of passwords, information system security, and data confidentiality.

## Data Quality Management and Monitoring

The Data Coordinating Center monitors CPCCRN studies on behalf of the investigators and the funding agency. The purposes of monitoring include demonstration of adherence to human subject protection requirements and assurance of high quality study data. Monitoring is done remotely. Remote monitoring involves detailed review of the data entered by the Clinical Center and telephone consultations with the Clinical Center investigator and/or research coordinator to review data quality. This requires uploading of complete consent documents and de-identified copies of specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the electronic data capture system.

## Record Access

The medical record must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the National Institutes of Health, and the Institutional Review Board (IRB) for each study site, if appropriate.

# Protection of Human Subjects

## Institutional Review Board (IRB) Approval

Institutional Review Board (IRB) approval will be obtained by the Data Coordinating Center (DCC) and each participating Clinical Center prior to enrolling patients into this study. This approval may be accomplished via a central IRB mechanism if this is available within the Network. The DCC will track IRB approval status at all participating centers

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and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

## Potential Risks and Benefits

There are no physical risks associated with participating in this study, as this is an obser- vational study and no therapeutic intervention is being tested. Biomarker measurements will be performed using blood that was already collected and remains unused after clinical laboratory testing is completed. There is a minor risk of loss of confidentiality. There is no immediate direct benefit to subjects enrolled in this study. The potential benefit to future patients is that more effective strategies for management and treatment of sepsis may be developed, leading to decreased mortality and improved quality of survival following severe sepsis.

## Protection against Risks

The risk of loss of confidentiality is mitigated by data security and confidentiality pro- cedures at the DCC that have been described. Dates of birth, death, hospital and PICU admission, hospital and PICU discharge, and dates of follow up evaluation will be recoded into days of age at each milestone prior to data analyses by investigators. During preparation of a public use dataset, required by the National Institutes of Health (NIH), the DCC will de-identify the data set.

## Informed consent and assent procedures

Parents or legal guardians of patients who meet eligibility criteria will be approached to obtain informed consent for participation in the study. Because many children with severe sepsis are too young and/or developmentally challenged, the primary outcome measures for LAPSE involve parent or guardian proxy-reporting for the quality of life instruments. Subjects who are developmentally capable of providing assent will be invited to participate in the study by providing self-report data for the primary outcome measure, PedsQL*T M* .

If a competent subject reaches the age of 18 years prior to completing the 12 month follow up, informed consent will be obtained from the subject for further study participa- tion.

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# Health Insurance Portability and Accountability Act

All study sites have been offered Business Associate Agreements (BAAs) with the Univer- sity of Utah. Copies of signed BAA are maintained at the DCC.

In accordance with NIH requirements, a public use dataset will be made available after completion of the study. This database will be completely de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

# Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled in all CPCCRN studies is a function of the underlying referral population at each Clinical Center selected by the National Institute for Child Health and Human Development (NICHD) to participate in the network. There will be no exclusion of patients based on gender, race, or ethnicity.

# Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory

authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

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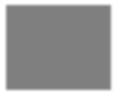
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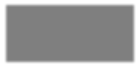
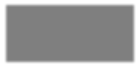
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LAPSE Study Protocol Overview





**Follow up** for surviving subjects

**Consented** Patients for LAPSE Study

**All** Community Acquired Severe Sepsis Patients

*Inclusion Criteria:*

SIRS variables, monitor and record organ failures, length of stay, PICU discharge status, hospital discharge status. DATASET 1

1. Two or more SIRS criteria
2. Suspicion of community acquired sepsis
3. Presence of arterial or central venous catheter
4. Cardiovascular failure
5. Pulmonary failure

Acute course data collection, treatment information, culture results, interventions used during PICU. DATASET 2

Individual and environmental modifiers. DATASET 3.

Baseline HRQL and functional status (FSS and POPC). DATASET 4

HRQL, FSS and POPC

seven and 28 days following PICU admission. DATASET 4

Three, six and 12 month evaluation by mail and telephone to include review of medical care since previous evaluation, HRQL. DATASET 5

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Approach ALL eligible subjects to obtain informed consent and assent.

Figure 1: Schematic summary of LAPSE Study.