

**Trichotomous Outcome Prediction in Critical Care
(The TOPICC Study)
CPCCRN Protocol Number 034**

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child
Health and Human Development (NICHD)

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Trichotomous Outcome Prediction in Critical Care

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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 Institutional 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

Critical care in general, and pediatric critical care in particular, have developed excellent measures of severity of illness calibrated to mortality. However, severity may be reflected in subsequent morbidity as well as survival. A major challenge of critical care outcomes research is the development of methodologies that predict the full range of outcomes from normal through the range of morbidities as well as death.

Critical care mortality prediction models are highly dependent on physiological system dysfunctions such as cardiovascular, neurological, respiratory, renal, metabolic, and hematological dysfunction. Yet the same dysfunction may result in intermediate and/or long-term functional status changes. ICU therapies such as steroid use and mechanical ventilation are associated with long-term sequelae including myopathy and chronic lung disease. It is logical to postulate that morbidity related to the progression of injury resulting from physiologic dysfunction such that, in the context of critical care, morbidity is an intermediate outcome between complete recovery and death.

The benefit from this study is the potential development and validation of a new predictive instrument to measure quality of care provided to children in PICUs across the country. This instrument will facilitate comparisons in quality of care and help inform the development of new interventions aimed at improving the quality of pediatric critical care. Advances would soon stimulate change in the neonatal and adult severity assessment methods. Historically, critical care methods have led the field of severity assessment and case mix adjustment; therefore, it is likely that this would further advance severity assessment methodologies throughout medicine. That would further stimulate advances in quality research and methods, case-mix adjustment methods, and forecasting outcomes, including the forecasting of long-term pediatric disability based on PICU admission data and how it is influenced by quality of care. Finally, this will add the determination of the probability of severe decreased functional status as well as death to the outcome probabilities, increasing the applicability and utility of these methods for decision making early in the PICU course.

1 Study Summary

1.1 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Determine the optimal time window in which to collect data elements representing the initial medical and physiological con-

dition of PICU patients at the time of admission to the PICU.

Specific Aim 2. Derive and validate a predictor of three or more outcome states following pediatric intensive care: death, survival with reduced functional status, and survival with normal or unchanged functional status.

1.2 Hypotheses

The hypothesis of this prospective observational project is that functional outcome (with at least three levels including death, survival with decreased functional status, or survival with normal or unchanged functional status) can be predicted from acute physiological status, acute and chronic diagnoses, chronic health status, and other information available during the first hours of pediatric critical care.

1.3 Primary Measure

The primary aim of this study is to derive and validate a statistical predictor of three or more outcome states from pediatric critical care, including death, survival with reduced functional status, and survival with normal or unchanged functional status. The success of this aim would fundamentally shift the paradigm of severity of illness assessment and quality methodologies.

1.4 Subject Eligibility

All patients under 18 years of age who are admitted to the PICU will be eligible and will be included in the probability sample for this study. Exclusion criteria are:

- Patient was admitted to the PICU previously during the current hospitalization; OR
- Patient does not have vital signs compatible with life for at least the first two hours after PICU admission.

1.5 Anticipated Accrual and Study Duration

This study will be a prospective observational cohort study of a probability sample of all patients under 18 years of age who are admitted to CPCCRN PICUs. The final sample size is estimated at 10,000 patients. The estimated duration of the study is two years.

2 Background and Significance

2.1 Pediatric Intensive Care Units (PICUs)

Numerous studies of the nature and characteristics of PICUs have been conducted. Such studies routinely emphasize that there is dramatic variability among PICUs in their patient populations, characteristics of care, and even organizational characteristics.¹⁻⁴ *Variability in morbidity among PICUs has NOT been studied.*

Remarkably, there have been few PICU studies including functional status of patients at the times of admission to and discharge from the PICU. Those that have been done indicate that many children are admitted to PICUs with functional disabilities and the discharge functional status is significantly worse than the admission status. A study from the medical PICU at Boston Children's Hospital of children with congenital and perinatal conditions found that 8% came from long-term or rehabilitation facilities, indicating that many children have diminished functional status on admission.⁵ A population-based study from the Syracuse, New York region found that 45% of all PICU admissions had special health care needs.⁶ Fiser et al found that 20% of patients in a selected sample had significant declines in their functional status by 6 months post discharge.⁷ A study from the United Kingdom used the Health Utilities Index 2 and found the average Health Utilities Index 2 was $0.73 \pm .01$ following PICU admission.⁸

2.2 Severity of Illness and Functional Status

Conceptually, severity of illness may be considered a continuous variable with extremes of outcomes (survival, death) occurring at low and high values; the threshold value determining the outcome is unknown and may vary from patient to patient. This concept of severity of illness has been exceptionally productive in pediatric, neonatal and adult intensive care.^{1-4, 9, 10} Even though there is great variability in PICUs, our current severities of illness methods have successfully adjusted mortality rates for the severity differences of different populations.

Intermediate outcomes associated with physiologic status (e.g. compromised functional status) may occur between the extremes and at different points on the severity of illness scale. There is no research on how initial severity of illness assessed by physiologic status is related to intermediate and long-term functional status. This study will explore and integrate this concept into severity of illness methodologies.

Extreme dysfunction of the magnitude that contributes to mortality risk also is associated with potential disability as well as death. Neurological injury as well as permanent effects on other individual organ systems may result from these physiologic deviations. Reductions in blood flow evidenced by blood pressure and heart rate changes, poor oxygenation, low blood sugar, poor coagulation, etc. increase the risk of neurological injury. Acute respiratory, cardiovascular, and renal failures risk long-term organ system dysfunction. Physiologic dysfunction is also correlated with length of PICU stay,⁴ increasing the “opportunities” for morbidities secondary to sepsis, infections, and other nosocomial insults.

Preliminary results from CPCCRN investigators have demonstrated the feasibility of this proposal.¹¹ At least four major reasons underline the need for the investigations proposed here:

1. Quantitative outcome studies using severity of illness are limited if only deaths are counted. Poor quality of care also causes damage without causing death.
2. Severity of illness adjusted evaluations may be biased by the “aggressiveness” of physicians to limit or withdraw care. Up to 50% of PICU deaths are in association with withdrawals and limitations of care.¹² Therefore, current methods that predict only survival and death as outcomes reward continued medical therapy for patients such as those in persistent vegetative states because they are counted as survivors.
3. There are outcome states (e.g. persistent vegetative state) that many individuals consider “worse than death”, yet these outcomes are not predicted by current severity of illness methods. If severities of illness methods are to develop into useful decision-making adjuncts for individual patients, they must assess the risks of other adverse conditions as well as mortality.
4. Severe disability has major economic and social consequences. There is a surprising paucity of data for non-neonates. ICUs may be a central source to the generation and maintenance of persons with very severely compromised functional status. Acute illnesses cared for in ICUs were estimated to include >20% of all profoundly retarded individuals.¹³ The continued costs of these infants and children are extensive. The yearly Medicaid reimbursable costs (1986 dollars) for each child requiring home care with a tracheostomy and oxygen were >\$64,000 and for those requiring mechanical ventilation at home >\$110,000.¹⁴

2.3 Classifying Functional Status and Outcomes

Large studies of adult injury classify outcomes into broad categories of death, vegetative/severely disabled functioning, and independence.¹⁵ Unfortunately, adult outcome scales have not been validated in children, have poor validation data, or do not account for the natural dependence of infants and children. In particular, their widespread use is prohibited because they are either too time consuming for large outcome studies and/or they are not applicable to the full age spectrum of infants and children in PICUs. Therefore, instruments such as the Glasgow Outcome Scale (GOS),¹⁶ Functional Independence Measure (FIM),¹⁷ the Level of Cognitive Functioning Scale (Los Ranchos Los Amigos Scale),¹⁸ and Rappaport's Disability Rating Scale¹⁸ are not suitable for routine use in PICUs.

There are difficulties with other measures of functioning of pediatric patients especially when their proposed use would be for large outcome studies. The Vineland Adaptive Behavior Scale (VABS) is too time consuming for a study of approximately 10,000 patients.¹⁹ Two other commonly used instruments in pediatric critical care for outcome assessment are the Pediatric Cerebral Performance Category (PCPC) Scale and the Pediatric Outcome Performance Category (POPC) Scale, which are modifications of the Glasgow Outcome Scale.^{20, 21} Unfortunately, classifications by raters requires substantial subjective projection. Additionally, there is no specific consideration of NG tubes, gastrostomies, technology dependence, specific motor findings, objective functional aids, medical equipment etc. Validation studies have demonstrated there is so much overlap in the categories that the CPCCRN does not consider their performances appropriate as a "research quality" outcome.⁷ This conclusion comes, in part, from previous experiences in modeling with these outcome assessments.

The previous development of the Functional Status Scale (Table 1 on the facing page), an objective, quantitative assessment of functional status at any given point in time, relevant to all ages of pediatric patients, as a measure analogous to the Activities of Daily Living Scale by the CPCCRN makes this proposal possible.²² It can be assessed from information in the medical records or from brief interviews and brief observation periods. Thus, it is appropriate for large outcome studies where detailed evaluations are not practical.

Table 1: Current Version of the Functional Status Scale (FSS)

	NORMAL (1)	MILD DYSFUNCTION (2)	MODERATE DYSFUNCTION (3)	SEVERE DYSFUNCTION (4)	VERY SEVERE DYSFUNCTION (5)
MENTAL STATUS	Normal sleep, wake, appropriate social responsivity	Sleepy but arousable to noise, touch, or movement; or periods of social non-responsivity	Lethargic and/or irritable	Minimal arousal to stimulus (stupor)	Unresponsive, comatose, or vegetative
SENSORY	Intact hearing and vision and responsive to touch	Suspected hearing or suspected vision loss	Non - reactive to auditory OR visual stimuli	Non - reactive to auditory AND visual stimuli	Abnormal response to touch
COMMUNICATION	Appropriate non-crying vocalizations, interactive facial expressiveness, or gestures	Diminished vocalization, facial expression or social responsiveness	Absence of attention getting behavior	No demonstration of discomfort	Absence of communication
MOTOR FUNCTION	Coordinated body movements, normal muscle control and awareness of actions	1 limb functionally impaired	2 or more limbs functionally impaired	Poor head control	Diffuse spasticity, paralysis, decerebrate or decorticate posturing
FEEDING	All food by mouth with age-appropriate help	NPO or need for age-inappropriate help with feeding	Partial or total tube feedings	Partial parenteral nutrition with enteral feedings	Total parenteral nutrition
RESPIRATORY	Room air, no artificial support or aids	Oxygen or suctioning	Tracheostomy	CPAP for all or part of the day or mechanical ventilation for part of the day	Mechanical ventilation support for all of the day and night

3 Preliminary Studies

3.1 Develop and Validate Trichotomous Outcome in PICU

Preliminary studies demonstrate the potential and the practicality of a trichotomous³ outcome predictor for PICU patients. The polychotomous logistic regression model was applied to 1131 patients from one of the primary investigator's national PICU data bases to model the prediction of ICU discharge as death (D), coma (C), and non-comatose survival (S).²⁰ Fitting a nominal model, the two discriminant functions with respect to the survivor group used PRISM, age, operative status, and diagnostic classification.

The observed/predicted patient numbers in the 3 outcome states were: Survivors - 959/959.08; Coma - 49/49.01; and deaths - 123/122.91. The goodness-of-fit of the model using Hosmer-Lemeshow^{23, 24} χ^2 statistics with the placement of the cutpoint between the (S) and the (C) outcomes (Table 2, and between the (C) and (D) outcomes (Table 3 on the facing page) indicate that this model fits quite well.

Table 2: Goodness-of-fit with cutpoint between survival and coma outcomes.

Predicted Risk \Rightarrow P(survival)	Survivor		Coma or Death	
	Observed	Expected	Observed	Expected
0.0 – 0.3	7	6.9	31	31.1
>0.3 – 0.6	38	35.9	37	39.1
>0.6 – 0.8	104	108.5	47	42.5
>0.8 – 0.95	406	407.3	49	47.7
>0.95 – 1.0	404	400.5	8	11.5
$\chi^2 = 2.07, p > 0.5$				

The area under the receiver operating curve (ROC) associated with the two dichotomies also indicated very good performance. For the classification into the groups (S) and (C)+(D), the area under the curve (AUC) = 0.842 \pm 0.019, while the classification into the groups (S)+(C) and (D) resulted in AUC = 0.863 \pm 0.021. To characterize the performance of the model when the outcomes of individual patients were predicted with respect to three categories, the decision thresholds of the dichotomies were systematically varied until Light's chance-corrected agreement $\chi^2 (A_p)$ ²⁵ attained a maximum. This resulted in the following decision algorithm:

Table 3: Goodness-of-fit with cutpoint between coma and death outcomes.

Predicted Risk \Rightarrow P(survival)	Death		Coma or Survivor	
	Observed	Expected	Observed	Expected
0.0 – 0.1	28	28.4	792	791.6
>0.1 – 0.25	30	28.3	150	151.7
>0.25 – 0.5	27	24.1	43	45.9
>0.5 – 0.75	24	26.6	19	16.5
>0.75 – 1.0	14	15.6	4	2.4

$\chi^2 = 2.52, p > 0.4$

$$Outcome = \begin{cases} (S) & \text{if } p(s) > 0.88 \\ (D) & \text{if } p(d) > 0.20 \\ (C) & \text{otherwise.} \end{cases}$$

The agreement χ^2 attained with this decision rule was $A_p = 276.9$, with 3 degrees of freedom, which is highly significant. The corresponding classification matrix, resulting in a value of Cohen's chance-corrected agreement index $\kappa = 0.35 \pm 0.03$, is shown in Table 4.

Table 4: Classification matrix based on survival, coma or death.

Predicted	Observed Outcome			Total
	(S)	(C)	(D)	
(S)	677	10	24	711
(C)	200	28	20	248
(D)	82	11	79	172
Total	959	49	123	
% Correct	70.6%	57.1%	64.2%	

A similar trichotomous outcome model was applied to 1663 patients classified by POPC as functional (F, normal and mild dysfunction) and compromised (C, moderate, severe, and vegetative).¹¹ The fitting ($p < .10$) of a nominal discriminant model used PRISM, age, operative status, admission

POPC, and diagnostic classification. The observed/predicted patient numbers in the 3 outcome states were: Functional - 1047/1047.0; Compromised - 507/506.95; and Dead - 109/109.05. The goodness-of-fit of the model by the two Hosmer-Lemeshow (as above) χ^2 statistics with the placement of the cutpoint between the (F) and the (C) outcomes (Table 5), and between the (C) and (D) outcomes (Table 6), indicate that this model fits quite well.

Table 5: Goodness-of-fit with cutpoint between functional and compromised outcomes.

Predicted Risk \Rightarrow P(survival)	Functional		Compromised or Death	
	Observed	Expected	Observed	Expected
0.0 – 0.3	6	8.1	391	388.9
>0.3 – 0.6	46	46.1	44	44
>0.6 – 0.8	303	298	106	111
>0.8 – 0.95	424	430.4	72	65.6
>0.95 – 1.0	268	264.5	3	6.5

$\chi^2 = 3.55, p > 0.3$

Table 6: Goodness-of-fit with cutpoint between compromised outcomes and death.

Predicted Risk \Rightarrow P(survival)	Death		Functional or Compromised	
	Observed	Expected	Observed	Expected
0.0 – 0.1	36	32.9	1351	1354.2
>0.1 – 0.25	24	28.1	157	152.9
>0.25 – 0.5	20	21.8	40	38.2
>0.5 – 0.75	15	13.8	6	7.2
>0.75 – 1.0	14	12.5	0	1.6

$\chi^2 = 3.32, p > 0.3$

The areas under the curve (AUC) associated with the two dichotomies were also very good. For the classification into the groups (F) and (C)+(D), the AUC = 0.902 ± 0.009 , while the classification into the groups (F)+(C) and (D) resulted in the AUC = 0.869 ± 0.022 . To characterize the performance of the model when the outcomes of individual patients were pre-

dicted with respect to three categories, the decision thresholds were selected according to the following algorithm:

$$Outcome = \begin{cases} (F) & \text{if } p(F) > 0.78 \\ (D) & \text{if } p(D) > 0.10 \\ (C) & \text{otherwise.} \end{cases}$$

The agreement χ^2 attained with this decision rule was $A_p = 512.8$, with 3 degrees of freedom, which is highly significant. The corresponding classification matrix, resulting in a value of Cohen's chance-corrected agreement index $\kappa = 0.42 \pm 0.02$, is shown in Table 7.

Table 7: Classification matrix based on functional, compromised, or death.

Predicted	Observed Outcome			Total
	(F)	(C)	(D)	
(F)	759	78	16	853
(C)	228	288	22	538
(D)	60	141	71	272
Total	1047	507	104	
% Correct	72.5%	56.8%	65.1%	

If only those children with (F) baseline functional status are considered, the % correct predictions of (F), (C), and (D) are 72.8%, 41.1%, and 56.1%, respectively. If only those children with a (C) baseline status are considered, the % correct prediction of (C) and (D) outcomes are 66.1% and 79.1% ((F) is not included since few children improve from a chronic compromised (C) state).

These pilot data support the study aim of developing an excellent polychotomous outcome predictor.

3.2 Development of Functional Status Score

The aim of this previous CPCCRN project was to develop a functional outcome measure suitable for large, pediatric outcome studies that is well defined, quantitative, sufficiently rapid, reliable, minimally dependent on subjective assessments, and applicable to the broad range of full term newborns to adolescents. The FSS is based on the conceptual frameworks of activities of daily living and adaptive behavior, selected with a consensus

process by a multidisciplinary group of health professionals from 11 institutions. Domains of functioning (Table 1 on page 13) were categorized from normal (one) to severe dysfunction (five) (range for total score six to 30). Clear definitions of all dysfunctional states were developed and included in the published manuscript.²² Patients from the CPCCRN institutions included:

1. pediatric intensive care unit (PICU) patients within 24 hours of PICU discharge;
2. high-risk non-PICU patients within 24 hours of hospital admission, and
3. technology dependent children.

Data included descriptive data, characteristics of care, and the FSS score.

The Adaptive Behavior Assessment System II (ABAS II), a validated questionnaire for the assessment of adaptive behavior, was utilized to establish construct validity and to provide calibration of the FSS scores within each domain. Bedside primary care nurses completed the ABAS II questionnaire based on their understanding of the patient's functioning when the FSS was completed. Patients from 10% of the study days were used to evaluate inter-rater reliability.

A total of 836 children were enrolled and had a wide range of functioning with an average FSS of 10.3 ± 4.4 . A total of 18% of all patients had the minimum FSS = 6 (best score), 44% had FSS ≥ 10 , 14% had a FSS ≥ 15 , and 6% had FSS scores ≥ 20 . The distribution of FSS scores is shown in Figure 1 on the facing page.

Each of the six FSS domains was highly significantly associated with the mean ABAS II ($p < .0001$). The performance of the FSS compared to the ABAS II was stable between the estimation and validation sets (Figure 2 on page 20). Discrimination was very good for both moderate and severe dysfunction and improved with FSS weighting (area under the ROC curve > 0.78). The investigators also reweighted the cell values in the FSS domains in the estimation set and tested this in the validation set, with slightly improved results. The correlations improved with the weighting from -0.58 in the estimation sample, and -0.60 in the validation sample (Table 8 on the facing page). The intraclass correlation of the unweighted and unweighted total FSS was 0.95 and 0.94.

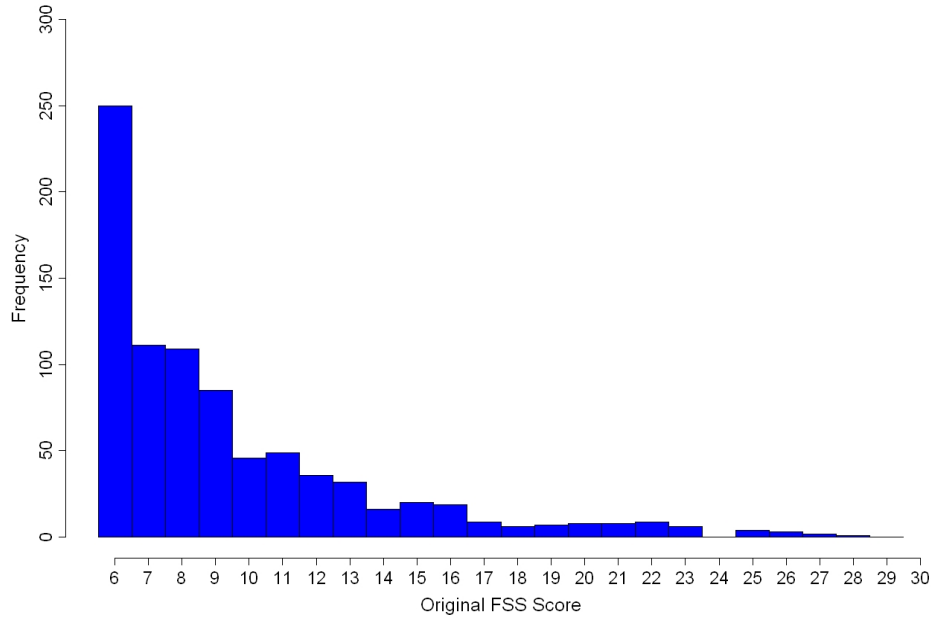


Figure 1: Distribution of Functional Status Scores (FSS)

Table 8: Correlation with ABAS II and areas under the ROC curve (AUC) for severe and moderate dysfunction.

	ABAS II Correlation	AUC ABAS II \leq 4 (severe dysfunction)	AUC ABAS II \leq 7 (moderate dysfunction)
Original FSS estimation	-0.58	0.83	0.79
Original FSS validation	-0.60	0.82	0.86
Weighted FSS estimation	-0.62	0.85	0.81
Weighted FSS validation	-0.63	0.83	0.87

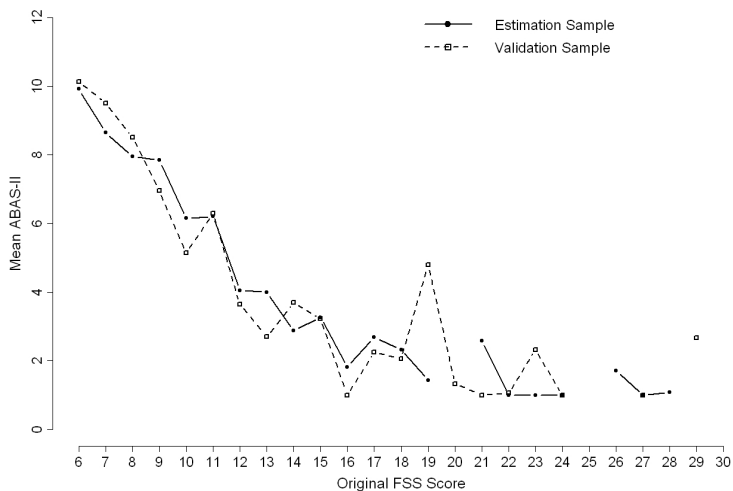


Figure 2: Correlation of ABAS II and total FSS score (unweighted)

4 Study Design and Methods

4.1 Patient Enrollment

A probability sample of consecutive patients will come from the participating PICUs of the CPCCRN. Ages newborn to <18 years will be included. Patients from all non-neonatal pediatric ICUs are eligible to be included, including general PICUs, cardiac PICUs, and neurological PICUs.

Patients may be admitted to the PICU multiple times during the same hospitalization, or in separate hospitalizations. Patients are eligible for inclusion in the TOPICC study only if selected in the probability sample for the first PICU admission in any specific hospitalization. Patients may be enrolled multiple times if the PICU admissions occurred in separate hospitalizations.

4.2 Categories and Timing of Data Collection

This study will collect information in the following different categories:

- Hospitalization:
 - Baseline Functional Status;

- Catastrophic Events During Hospitalization;
- Functional status at time of hospital discharge;
- Functional status at Day 28 post-PICU discharge (when applicable)(Phase 1 only);
- Hospital discharge (in survivors);
- Hospital death (when applicable);
- PICU course (first during hospitalization):
 - PICU admission information;
 - Physiological information;
 - Functional status at time of PICU admission (Phase 1 only);
 - PICU care process information;
 - Limitations or withdrawal of care discussions (when applicable);
 - Surgery during PICU course (when applicable);
 - Cardiac surgery information associated with PICU admission or course (when applicable);
 - Cardiopulmonary resuscitation associated with PICU admission or course (when applicable);
 - Functional status at time of PICU discharge (when applicable);
 - PICU discharge information (when applicable).

Note that when a subject is enrolled into TOPICC during multiple separate hospitalizations, there will be multiple records in the electronic data capture (EDC) system. However, when a subject has multiple PICU admissions within the same hospitalization, the patient is only eligible for enrollment if selected in the probability sample on the first PICU admission. Subsequent PICU admissions during the same hospitalization are not eligible for inclusion in the study.

4.3 Data Elements

The data elements to be collected are described in the following sections. Certain data elements have standard definitions (such as race), and other data elements may be coded similarly to previous studies. The tentative coding is indicated in the sections below, but the final coding may differ from what is listed here. If *new* data elements are added to the study, an amendment will be submitted to the Institutional Review Board for prior approval.

4.4 Hospitalization

Demographic and historical data for each hospitalization include the following elements:

- Date and time of hospital admission;
- Date of birth;
- Gender;
- Race and ethnicity (standard definitions);
- Primary language (English, Spanish, or other)(Phase 1 only);
- Payer (standard definitions);
- Residential zip code;
- Date and time of emergency department admission (if applicable);
- Catastrophic condition prior to hospital admission (yes or no);
- If yes to catastrophic event, description and time interval since event;
- Known mental retardation or developmental delay (yes or no);
- Subject enrolled in TOPICC study during a previous hospitalization (yes or no);
- If yes, enter the EDC subject ID for the first enrollment.

4.4.1 Baseline Functional Status

- FSS prior to hospital admission (from medical record or clinical caretaker);
- POPC and PCPC prior to hospital admission (from medical record or clinical caretaker);

4.4.2 Catastrophic Events during Hospitalization

- Date and time of catastrophic event;
- Catastrophic event.

4.4.3 Hospital Discharge

- Hospital discharge date and time, if survivor;
- Catastrophic events during hospitalization (yes or no);
- FSS, POPC, and PCPC in survivors at hospital discharge;
- Discharge location;
- Discharged to hospice care (yes or no);
- Day 28 post-PICU discharge date and time (if applicable)(Phase 1 only);

- FSS, POPC, and PCPC in survivors at Day 28 post-PICU discharge (if applicable)(Phase 1 only).

In addition to the listed data elements, the final discharge ICD-9 diagnosis and available procedure codes, Diagnosis Related Group (DRG), and Major Diagnostic Category (MDC) will be obtained from the final coding by the hospital. These codes are distinct from physician-assigned codes that may have been used for physician billing, which are not being collected.

For each functional assessment (in survivors), the information was obtained from the following sources (check all that apply):

- Medical record;
- Clinical caretaker;
- Direct observation.

At the time of functional assessments, relevant medication data elements that will be collected include:

- Neuromuscular blockade in the 24 hours prior to the hospital discharge FSS assessment (yes/no);
- Sedatives within previous 4 hours (yes/no);
- Narcotics within previous 4 hours (yes/no);
- Other pain medications within previous 4 hours (yes/no);
- Sleeping aids within previous 4 hours (yes/no);
- Other drugs affecting functional status within previous 4 hours (yes/no).

At the time of functional assessments, other relevant factors to be collected include:

- Arm and/or foot boards preventing extremity function (yes/no);
- Soft or hard restraints preventing extremity function (yes/no);
- Bandages or casts preventing extremity function (yes/no);

4.4.4 Hospital Death (when applicable);

For those patients dying in the PICU or in the hospital, the study will collect:

- Date and time of death;
- Location (PICU, step-down unit, hospital general care unit, other);

- CPR administered (yes or no);
- Mode of death (Failed resuscitation, withdrawal of care, limitation of care, brain death);
- Medical examiner case (yes or no);
- Autopsy requested (yes or no);
- Autopsy performed (yes or no);
- Location autopsy performed (Medical examiner's office, hospital, other);
- Reason autopsy not performed (Physician did not offer option of autopsy to parent, physician offered option of autopsy but parent refused);
- Organ donation offered (yes or no);
- Organ donation occurred (yes or no);
- Organ donation occurred following brain death or cardiac death;
- If donation occurred, organs donated (all that apply from heart, liver, kidneys, pancreas, intestines, other).

4.5 PICU Course

4.5.1 PICU Admission Information

PICU admission data include the following elements:

- Date and time of PICU admission;
- Admission status (elective or emergency);
- Patient admitted for postoperative care (yes/no);
- For postoperative admissions, type (Cardiac, interventional cardiac catheterization, neurosurgery, orthopedic, transplant, trauma, general surgery, ENT, other (specify));
- Clinical service with primary responsibility;
- Admission source (Direct admission from outside of the study hospital, study hospital emergency department, study hospital general care floor, study hospital intermediate care unit, study hospital other ICU, study hospital monitoring unit, study hospital operating room, study hospital other location);
- Primary and secondary acute diagnoses based on admission notes;
- Chronic diagnoses based on admission notes;
- Nurse to patient ratio for PICU admission shift;
- Nurse to patient ratio for 2nd (next) PICU shift.

For patients admitted with primarily cardiovascular disease (acquired or

congenital heart disease), diagnoses and procedures will be assessed from the cardiology and/or cardiovascular surgery medical record entries:

- Acquired heart disease (all that apply at time of PICU admission);
- Congenital heart disease (all that apply at time of PICU admission)

4.5.2 Physiological Status

The most detailed data elements concern the initial medical and physiological status of the patient early in the PICU admission, but determining the optimal time interval for collecting these data is the goal of Specific Aim 1. During the initial phase of this study (Phase 1), medical and physiological data elements, including laboratory tests, will be obtained from four hours prior to PICU admission through 12 hours post-PICU admission. After the optimal time interval has been determined from analyses of data obtained from the first 50 children at each site, that time interval will be used in subsequent data collection (Phase 2). Based on the data analyses from Phase 1, it has been determined that two hours prior to PICU admission through four hours post-PICU admission is the optimal time window for data collection.

With the exception of laboratory parameters, physiological data will not be collected during the operating room (OR) period. This is because a) the data are profoundly influenced by anesthesia; b) illness from the OR should be reflected in the physiological status in the PICU postoperatively; and c) our goal is not to assess OR quality of care.

In Phase 1 (approximately the first 50 enrolled subjects from each CPCCRN site), laboratory parameters will be comprehensively recorded (all measurements obtained during the period from 4 hours prior to 12 hours after PICU admission, including the OR period) and will include the measured value, date and time of the measurement. The parameters include:

- pH (arterial, venous, or capillary);
- PCO₂ (arterial, venous, or capillary);
- total CO₂;
- P_aO₂ (arterial only);
- Glucose;
- Potassium;
- Blood urea nitrogen (BUN);
- Creatinine;

- Calcium (total);
- Calcium (ionized);
- Albumin;
- Sodium;
- Hemoglobin;
- White blood cell total count (WBC);
- Platelet count;
- PT;
- PTT;
- INR.

In Phase 2, laboratory parameters will be recorded during the time period determined after the analyses for Specific Aim 1, but only selected values (as indicated below) will be collected. The date and time of laboratory measurements in this phase will *not* be recorded.

- pH (arterial, venous, or capillary) (highest and lowest);
- PCO₂ (highest);
- total CO₂ (highest and lowest);
- P_aO₂ (arterial only) (lowest);
- Glucose (highest and lowest);
- Potassium (highest);
- Blood urea nitrogen (BUN) (highest);
- Creatinine (highest);
- Calcium (total) (highest and lowest);
- Calcium (ionized) (highest and lowest);
- Sodium (highest and lowest);
- Hemoglobin (highest and lowest);
- White blood cell total count (WBC) (highest and lowest);
- Platelet count (lowest);
- PT (highest);
- PTT (highest);
- INR (highest).

In Phase 1, the following physiological parameters will be recorded *with* the date and time of the observation (but omitting data during the operating room (OR) period in surgical patients); in Phase 2, the same parameters will be recorded *without* the date and time of the observation:

Measurements obtained during the period from 0 to 12 hours after PICU

admission include:

- Systolic blood pressure (highest and lowest);
- Heart rate (highest and lowest);
- Temperature (highest and lowest);
- Respiratory rate(highest and lowest)
- GCS motor response (worst);
- GCS total (worst);
- Level of consciousness (worst);
- Pupillary reflexes (worst);
- Patient appears to have acute neurological injury (yes or no).

The GCS motor response should reflect the response in the absence of neuromuscular blockade or significant sedation. For example, if the child has decorticate posturing, and then receives neuromuscular blockade, the GCS motor response should NOT be one - it should be three.

The total GCS value may be obtained at a time that the child has an endotracheal tube, in which case the verbal score is an obligatory value of one. Thus, the presence of an endotracheal tube at the time of GCS assessment will be recorded.

For pupillary responses, we will record whether the child is hypothermic (below 34 °C, yes or no).

4.5.3 Functional Status at PICU Admission (Phase 1 only)

- FSS at time of PICU admission (from medical record, clinical caretaker, and/or direct observation);
- POPC and PCPC at time of PICU admission (from medical record, clinical caretaker, and/or direct observation);

For each functional assessment, the information was obtained from the following sources (check all that apply):

- Medical record;
- Clinical caretaker;
- Direct observation.

At the time of functional assessments, relevant medication data elements that will be collected include:

- Neuromuscular blockade within previous 7 days (yes/no);
- Sedatives within previous 4 hours (yes/no);
- Narcotics within previous 4 hours (yes/no);
- Other pain medications within previous 4 hours (yes/no);
- Sleeping aids within previous 4 hours (yes/no);
- Other drugs affecting functional status within previous 4 hours (yes/no).

At the time of functional assessments, other relevant factors to be collected include:

- Arm and/or foot boards preventing extremity function (yes/no);
- Soft or hard restraints preventing extremity function (yes/no);
- Bandages or casts preventing extremity function (yes/no);

4.5.4 PICU Care Processes

Care process data elements will be collected to describe the overall population, as well as to help manage data collection of supplemental data when applicable. During the PICU stay, did any of the following occur at any time (yes or no):

- Mechanical ventilation;
- High frequency ventilation (oscillator or jet);
- Nitric oxide;
- Intracranial pressure monitoring;
- Therapeutic hypothermia;
- Vasoactive infusions;
- Antibiotic administration;
- Steroid administration;
- Neuromuscular blockade;
- Extracorporeal support (ECMO or VAD);
- Renal replacement therapy (hemofiltration or dialysis);
- Parenteral nutrition;

4.5.5 Limitations or Withdrawal of Care Discussions

If there were discussions or decisions involving limitations or withdrawals of care, regardless of whether the patient ultimately died, data in this section will be collected. Data should be obtained for such discussions or decisions that occurred during current PICU admission. Note that discussions of these end of life topics may have been held without ultimately deciding to limit or withdraw care. In these circumstances, the questions in this section are still expected to be answered.

Information about discussions with the family:

- Date and time first discussion took place concerning limitation or withdrawal of care;
- Date and time when limitation or withdrawal of care was first discussed in the medical record;
- Palliative care consultation (yes or no, if yes date and time);
- Pain service consultation (yes or no, if yes date and time);
- Ethics consultation (yes or no, if yes date and time).

Limitations of future care will be recorded as yes or no, and include:

- Mechanical ventilation;
- Vasoactive medications;
- Cardiac compressions;
- Extracorporeal Membrane Oxygenation (ECMO) or Ventricular Assist Device (VAD);
- Dialysis / other renal replacement therapy.

Withdrawals of already instituted care in anticipation of death will be recorded as yes or no, and include:

- Discontinuation or weaning of mechanical ventilation;
- Discontinuation or weaning of vasoactive medications;
- Discontinuation of fluids or feeding;
- Discontinuation of extracorporeal support (ECMO or VAD);
- Discontinuation of renal replacement therapy;
- Other (specify).

4.5.6 Surgery during PICU Course

For patients receiving an operation while in the PICU (not prior to admission), the following data will be collected:

- Date and time of surgery;
- Date and time patient arrived in PICU after surgery;
- Elective or emergency surgery;
- Type of surgery (Cardiac, interventional cardiac catheterization, neurosurgery, orthopedic, transplant, trauma, general surgery, ENT, other);
- Name of surgery;
- Nurse to patient ratio for PICU shift when patient returned from surgery;
- Nurse to patient ratio for 2nd (next) PICU shift after return from surgery.

During Phase 2, the following laboratory tests will be recorded during the time period established from the Phase 1 analysis, without date or time:

- pH (arterial, venous, or capillary) (highest and lowest);
- PCO₂ (highest);
- total CO₂ (highest and lowest);
- P_aO₂ (arterial only) (lowest);
- Glucose (highest and lowest);
- Potassium (highest);
- Blood urea nitrogen (BUN) (highest);
- Creatinine (highest);
- Calcium (total) (highest and lowest);
- Calcium (ionized) (highest and lowest);
- Sodium (highest and lowest);
- Hemoglobin (highest and lowest);
- White blood cell total count (WBC) (highest and lowest);
- Platelet count (lowest);
- PT (highest);
- PTT (highest);
- INR (highest).

In the 12 hours after return from surgery to the PICU (Phase 1) or the time period established by Phase 1 analysis (during Phase 2), the following

variables will be collected (without date and time):

- Systolic blood pressure (highest and lowest) (Phase 2 only);
- Heart rate (highest and lowest) (Phase 2 only);
- Temperature (highest and lowest) (Phase 2 only);
- Respiratory rate (highest and lowest) (Phase 2 only);
- GCS motor response (worst);
- GCS total (worst);
- Level of consciousness (worst);
- Pupillary reflexes (worst);
- Patient appears to have acute neurological injury (yes or no).

Note that the 12 hour intervals described above are during Phase 1, and may be altered in response to the analyses conducted with respect to Specific Aim 1, which will determine the optimal window in which to collect these variables.

The GCS motor response should reflect the response in the absence of neuromuscular blockade or significant sedation. For example, if the child has decorticate posturing, and then receives neuromuscular blockade, the GCS motor response should NOT be one - it should be three.

The total GCS value may be obtained at a time that the child has an endotracheal tube, in which case the verbal score is an obligatory value of one. Thus, the presence of an endotracheal tube at the time of GCS assessment will be recorded.

For pupillary responses, we will record whether the child is hypothermic (below 34 °C, yes or no).

4.5.7 Cardiac Surgery

For patients undergoing cardiovascular surgery immediately prior to or following PICU admission, the following data from the operation will be collected:

- Date and time of operation;
- Cardiac surgery immediately prior to or after PICU admission;
- Bypass time (when applicable);

- Cross clamp time (when applicable);
- Deep hypothermia with cardiac arrest time (when applicable);
- Unplanned cardiac arrest (yes or no);
- Vasoactive drips at time of discharge from operating room (yes or no);
- ECMO used at time of discharge from operating room (yes or no);
- VAD used at time of discharge from operating room (yes or no);
- Chest remained open at the time of discharge from operating room (yes or no);
- Lactate value drawn after arrival in ICU from surgery (first);
- pH value obtained after arrival in ICU from surgery (first);
- Upload de-identified cardiac operative report.

For children discharged from the operating room on vasoactive drips (the large majority), the vasoactive drugs being infused on admission to the PICU will be recorded without dosage information.

4.5.8 Cardiopulmonary Resuscitation

For patients who receive open or closed chest cardiopulmonary resuscitation (CPR) (compressions or defibrillation), the following information will be recorded for each occurrence that is separated by at least 20 minutes of spontaneous circulation. For children who do not have return of spontaneous circulation for at least 20 minutes, only the initial episode requires data entry:

- Date and time of event;
- Chest compressions (yes or no);
- If chest compressions, date and time of start;
- If chest compressions, date and time of stopping;
- If chest compressions, compressions started for a) poor perfusion (i.e. bradycardia, hypotension), or b) pulselessness.
- Defibrillation (yes or no);
- Return of circulation (yes or no);
- ECMO used to achieve ROC (yes or no);
- Alive at 24 hours after CPR (yes or no).

4.5.9 Functional Status at PICU Discharge

- FSS at time of PICU discharge, in PICU survivors;
- POPC and PCPC at time of PICU discharge, in PICU survivors;

For each functional assessment, the information was obtained from the following sources (check all that apply):

- Medical record;
- Clinical caretaker;
- Direct observation.

At the time of functional assessments, relevant medication data elements that will be collected include:

- Neuromuscular blockade in the 24 hours prior to the PICU discharge FSS assessment (yes/no);
- Sedatives within previous 4 hours (yes/no);
- Narcotics within previous 4 hours (yes/no);
- Other pain medications within previous 4 hours (yes/no);
- Sleeping aids within previous 4 hours (yes/no);
- Other drugs affecting functional status within previous 4 hours (yes/no).

At the time of functional assessments, other relevant factors to be collected include:

- Arm and/or foot boards preventing extremity function (yes/no);
- Soft or hard restraints preventing extremity function (yes/no);
- Bandages or casts preventing extremity function (yes/no);

4.5.10 PICU discharge

- PICU discharge date and time;
- Surgical procedure after PICU admission;
- Cardiopulmonary resuscitation (chest compressions and/or defibrillation);
- Limitation or withdrawal of care discussed or instituted (yes or no);
- Patient alive at time of discharge (yes or no);
- Discharging clinical service;
- Receiving clinical service(Phase 1 only);
- Transfer location (Step-down unit, hospital general care unit, another ICU in the same hospital, in-patient rehabilitation, chronic care facility, another hospital, home);
- Primary and secondary acute diagnoses based on discharge notes;

- Chronic diagnoses based on discharge notes.

4.6 Sample Size

The pilot data (Section 3 on page 14) indicate that the number of new, low functional status states at PICU discharge will be at least equivalent to the number of deaths. Since the pilot study did not include a high risk group (cardiovascular surgery), it is likely that the incidence is higher. Additionally, pediatric trauma data indicate that 16.5% of head trauma survivors admitted to the PICU have discharge VABS scores > 2 S.D.s below the mean. Sample size requirements to detect a given effect are highly dependent on various prevalence and rate assumptions. For example, using logistic regression models, if poor outcome occurs in 4% of patients without a factor present, then only 431 patients are required to detect an odds ratio of 3 for poor outcome associated with the presence of the factor if one-half of subjects have that factor, but 990 patients if only 10% have that factor, and 1816 if the factor is present in only 5%. Therefore, having several thousand patients available for the primary analysis is necessary to assess potential effects of relatively uncommon categorical factors. In multivariable models, it is also necessary to have sufficient numbers of patients with events, approximately 12-13 patients/death/predictor variable. Thus, for a mortality rate of 4.0%, the total sample size needed for the study would be approximately 6500 patients, by this general criterion. We will use an additional of approximately 3500 subjects for model validation. Thus, the total planned sample size for this study is approximately 10,000 patients.

5 Data Analysis

Specific Aim 1. Determine the optimal time window in which to collect data elements representing the initial medical and physiological condition of PICU patients at the time of admission to the PICU.

The optimal time period for data collection is unknown. Ideally, the data collection would be as short as possible to separate the effect of therapy from physiology. Therefore, the most narrow time period without biasing individual sites will be sought. The time period should include a short pre-admission time period to include “admission” labs that are obtained shortly before admission. However, the time period should be long enough to insure that there is no practice pattern variability in the sampling of laboratory data. It is anticipated that these time periods vary among institutions.

Therefore, we will determine the times of collection and values of variables from 4 hours prior to ICU admission to a maximum of the first 12 hours after ICU admission. (The maximum of 12 hours is chosen because the existing methodology, PRISM III, uses a maximum time period of 12 hours that was determined using a similar methodology over 10 years ago.)

These data will be collected for 50 consecutive patients at each site. For Specific Aim Two, the study will focus on the time period where 90% of most abnormal physiological variables will have been collected without biasing individual sites.

Specific Aim 2. Derive and validate a predictor of three or more outcome states following pediatric intensive care: death, survival with reduced functional status, and survival with normal or unchanged functional status.

Variables to be considered for inclusion into the outcome prediction model are:

- PRISM with and without neurological variables: Physiologic variables will be included as the PRISM III score based on the excellent results in the preliminary studies. We will divide the PRISM III score into the score without the neurological variables and the PRISM III with neurological variables only (mental status/GCS and pupillary reflexes are included in the PRISM III score). Other components of the PRISM III score are cardiovascular, respiratory, metabolic, renal, and hematological. Specifically we do not plan on including other elements of the neurological examination because these are so frequently altered by sedation, paralytics, and other drugs in the PICU, that they are unreliable.
- location from which the patient was transferred (routine care area, other ICU), outpatient facility)
- operative status (emergency and elective)
- diagnoses (up to 6 diagnoses as categorical variables)
- age
- baseline FSS

It is expected that additional variables that are potentially predictive are likely to arise as the analysis progresses. We will investigate the predictive

potential of up to 20 variables. The outcomes of primary interest are PICU and hospital discharge outcomes (mortality and functional status).

The initial analyses will focus on the relationship of the independent variables with the Functional Status Scale. First, we will assess the relationship of functional status at hospital discharge to initial hospital functional status. Diagnosis, surgery, physiologic instability (PRISM III score), steroid use, sedation, paralysis, length of stay, known complications, etc) will be used to help guide this effort. Dichotomous analyses will assess whether or not the survival with low function status, survival with non-low functional status, and death are associated with the independent variables. For continuous (e.g. PRISM) and ordinal predictors variables, the two-sample t test and/or Kruskal-Wallis test will be used. For nominal or categorical variables (e.g. diagnoses) the χ^2 or Fisher's exact test will be used. In addition, we will similarly examine association of factors with the three-level ordered outcome, using appropriate tests (e.g., Mantel-Haenszel χ^2 test, Jonckheere-Terpstra test) that take the ordering of the outcome and when applicable the potential predictor into account.

Our initial models will assume that functional status is a linear scale with death and normal outcome being the extremes. Linear regression techniques will be used for this "simple" model. We will investigate the model performance by categorizing the observed and predicted outcomes into 3 or more functional categories (e.g. normal and mild, moderate, and severe dysfunctions, and death).

More advanced models will utilize polychotomous logistic regression. This can be divided into two cases: ordinal response and nominal response. The proposed outcomes of death, survival with low-functioning, and survival with adequate functioning apply best to ordinal data. For ordinal data, cumulative logits can be modeled with the proportional odds model (PROC LOGISTIC of the SAS System). If the proportional odds (parallel regression lines) assumption is not satisfied, then generalized logits approach will be used (PROC CATMOD of SAS). Since the referral patterns of individual PICUs may attract clusters of specific types of patients, the Generalized Estimating Equations (GEE) methodology will be used for multiple regression analysis and/or polychotomous logistic regression analysis to adjust for clusters effect and missing data (PROC GENMOD of SAS). Since there are only eight CPCCRN hospitals (clusters), an appropriate small-cluster correction will be implemented for these models^{26, 27}

The independent variables associated with outcomes using a liberal inclusion criterion (e.g. $p < .3$) will be entered into the polychotomous multiple logistic regression model to determine the partial (adjusted for other

variables) association of each variable with outcome. Variables that show association in the univariate analysis but little additional predictive ability after adjustment for others will be removed from the model. When possible, likelihood-based criteria will be used to facilitate decisions to retain or remove a variable, although in some instances a variable showing slightly less predictive ability than a competitor might be retained if that variable is substantially easier to collect/assess, or has substantially less missing data.

Goodness-of-fit assessment of polychotomous logistic regression models has not been developed into an easily accessible form and thus initially the approach proposed by Begg and Gray²⁸ and recommended by Hosmer and Lemeshow²⁹ will be followed. This method assesses the fit by calculating logistic regression diagnostics of individual dichotomous classifications. For a trichotomous outcome variable, the assessment of fit of the outcome probabilities obtained by two discriminant functions is illustrated in the pilot studies discussed in Section 3 on page 14 (e.g. predicting (death + low-functional status) vs. survival with non-low functional status; death vs. all survivors). This approach is also well suited for the potential applications of the outcome predictor including quality assurance and decision analysis aids.

Recently, Hosmer and colleagues have extended their general approach to goodness-of-fit assessment to logistic models with multinomial outcomes,³⁰ and we will implement this approach for assessing goodness of fit of our models. This may be challenging if GEE is used to account for center effect, although likely this method is extendable as was done for standard logistic regression.³¹

The prognostic performance will be evaluated by ROC analysis of the dichotomy of primary concern (e.g. (death + low-functional status vs. survival). The AUC will be used as a performance measure, which has well-known interpretive meaning and statistical properties.

Predictor characteristics applied to individual patients will be further evaluated with Cohen's chance-corrected agreement (κ).³² This index can be applied to either nominal or ordinal categories.³³ It also provides the flexibility that if utilities are assigned to the various correct³⁴ and incorrect classifications, an appropriately weighted κ statistic can be achieved. Quality of life issues especially for children with neurodevelopment issues is an evolving and important issue that can be addressed both with this data set and this methodology.³⁵

We will also explore other analytic approaches. First, for conditions resulting in a high incidence of loss of functional status (e.g. CNS disease, CPR, congenital heart disease surgery), condition-specific predictors of out-

come may be appropriate. In particular, prediction of outcome following congenital heart disease surgery is likely to be optimized by considering this patient group separately. Second, for conditions where the incidence of dependency displays very little change over the hospitalization (e.g. patients admitted in dependent states as their baseline), a two outcome predictor (survival in baseline condition and death) may be most appropriate. Third, some diagnostic groups will yield very small (<1%) fractions of patients in either the dependent or death categories. “Table shrinking” toward the pooled mortality rate of these low-incidence diagnostic groups may be applied to obtain more precise estimates for each group.³⁶

6 Data Management

6.1 Electronic Data Capture System

Data will be collected at each clinical site and entered into the electronic data capture (EDC) system implemented by the Data Coordinating Center. All research coordinators and investigators will be trained to use this system prior to implementing the study.

6.2 Data Security

The DCC is located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, and separate air filtering. 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 intrusion 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 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using SSL or VPN technologies, both of which provide at least 128 bit encryption. The electronic data capture system(EDC), 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 reg-

ularly run against DCC servers, and DCC IT staff are notified of intrusion alerts.

Servers are backed up daily through a dedicated backup server that connects across an internal Gigabyte network to a robotic tape drive. Incremental backups occur hourly Monday thru Friday from 6am to 6pm. Incremental backups are also performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the server room, and full backups are taken off site on a weekly basis. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 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.

6.3 Data Confidentiality

The investigators and staff of the DCC are fully committed to the security and confidentiality 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 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.

6.4 Data Quality Management and Monitoring

6.4.1 Data Monitoring

The DCC will assign clinical data managers to address issues of on-going data quality as data are submitted throughout the study. Automatic and manual queries will be generated using the computerized Query System to help resolve data discrepancies and an audit trail will be maintained for all changes made to the study database.

6.4.2 Site Monitoring

Site monitors may be sent by the DCC to clinical sites to help assure regulatory compliance, improve the quality of data collection and management

at each site, and to provide education to site coordinators and investigators (if needed). The site monitors will be DCC staff or hired via a subcontract. Monitoring reports will be sent to the DCC and will be available to NICHD staff.

When site monitoring visits occur, the monitor will inspect the Essential Documents Binder, which contains IRB documents, investigator licenses, and other required materials. The monitor will examine the IRB documents and verify that the IRB approval is valid for the current version of the study protocol. The monitor will also examine selected subject study files, and will conduct source verification on selected data elements.

6.4.3 Remote Monitoring

Physical site monitoring is expensive, and will be supplemented with remote monitoring by DCC study coordinators. The DCC will identify selected data elements for remote monitoring and notify the clinical sites to fax the source documents for those data elements to the secure fax server at the DCC. The source documents will be compared to the data entered into the electronic data capture system at the DCC. Sites that have high accuracy will be monitored less frequently than sites with less ideal performance.

7 Protection of Human Subjects

Potential Risks and Benefits: There are no major risks associated with participating in this study, as this is an observational study and no therapeutic intervention is being tested. There is a minor risk of loss of confidentiality. The benefit from this study is the potential development and validation of a new predictive instrument to measure quality of care provided to children in PICUs across the country. This instrument will facilitate comparisons in quality of care and help inform the development of new interventions aimed at improving the quality of pediatric critical care. Advances would soon stimulate change in the neonatal and adult severity assessment methods. Historically, critical care methods have led the field of severity assessment and case mix adjustment; therefore, it is likely that this project will further advance severity assessment methodologies throughout medicine. That would further stimulate advances in quality research and methods, case-mix adjustment methods, and forecasting outcomes, including the forecasting of long-term pediatric disability based on PICU admission data and how it is influenced by quality of care. Finally, this will add the determination of the

probability of severe decreased functional status as well as death to the outcome probabilities, increasing the applicability and utility of these methods for decision making early in the PICU course.

Protection Against Risks: Patient information is sent to the DCC to enable proper data validation and accurate coding of such data as the age of patients. To prepare the analytical database, the DCC will recode all such patient identifiers, and create a de-identified data set in accordance with definitions of the Health Insurance Portability and Accountability Act (HIPAA). This analytical database will be the only one available for the analysis of the current and future derivative studies.

Informed Consent: Since the study design is a daily review of existing information in the medical record and carries minimal risk to the patient, waiver of informed consent is requested. The scientific validity of this study requires completely unbiased enrollment of subjects, and enrollment of all admissions (or a large probability sample of all admissions) into the study would make informed consent impractical.

8 Health Insurance Portability and Accountability Act

The abstracted data will be de-identified with respect to patient identifiers. Dates will be recoded after entry into the EDC to provide the age, and the DCC will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All study sites have been or will be offered Business Associate Agreements (BAA) with the University of Utah. Copies of signed BAA are maintained at the DCC.

9 Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled in all CPC-CRN 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.

10 Access to and Retention of Records

Records relating to the research, including subject study files and medical records, must be available for inspection of authorized site monitoring personnel from the Data Coordinating Center, or authorized representatives of Federal regulatory or funding agencies.

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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APPENDIX - FSS Domain Cell Definitions

The Mental Status, Sensory, Communication and Motor functions should be based on the best functioning over the last 4 hours prior to the assessment. The Feeding functions should be based on the last 12 hours prior to the assessment. The Respiratory functions should be based on the last 24 hours prior to the assessment. Appropriate information sources include direct observation or information conveyed by other reliable health care providers.

MENTAL STATUS

Normal

- Normal sleep and wake periods;
- Appropriate social responsiveness

Sleep refers to a restful state without over-reaction (crying, agitation) to noises in the environment. Awake refers to awareness with behavior appropriate for age. Infants and children in this state should be appropriately aware, alert and responsive of self and environment.

Mild Dysfunction

- Sleepy but arousable to noise or touch or movement, and/or
- Periods of reduced social responsiveness

Sleeps more of the time than is age appropriate; will sleep much of time if left alone but is able to be aroused with stimulation such as noise, if touched or position changes. Alternatively, decreased responsiveness to social overtures and/or does not consistently focus on or follow a person or object crossing the line of vision.

Moderate Dysfunction

- Lethargic and/or
- Irritable

Lethargic infants and children are drowsy, sluggish, or have an unusual lack of energy. They are arousable, but become less responsive or return to a sleep-like state without frequent stimulation. Irritable infants and children are inconsolable often with an increased sensitivity to stimulation. Infants often react to stimuli with a high-pitched cry.

Severe Dysfunction

- Minimal arousal to stimulus (stupor)

Stuporous infants and children have decreased or impaired consciousness marked by diminution in reactions to environmental stimuli. They may open

eyes and focus, but do not maintain any meaningful reaction to physical environment. They make little or no eye contact. They will respond to noxious stimuli with semi-purposeful (i.e. poorly organized) movements or withdrawal.

Very Severe Dysfunction

- Unresponsive and/or
- Coma and/or
- Vegetative

These infants and children are unconscious. Coma is a deep or profound state of unconsciousness from which they cannot be aroused. They do not sense or respond to external stimuli or internal needs. Vegetative infants and children have no evidence of awareness of self or environment. They may have intermittent wakefulness manifested by sleep- wake cycles. There is no evidence of sustained, reproducible, purposeful or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli.

SENSORY

Normal

- Intact hearing, and
- Intact vision, and
- Responsive to touch or pain

Intact hearing is demonstrated by individuals localizing/ moving eyes and/or head toward sound stimulus in room. Intact vision is evidenced by individuals turning gaze to focus on person or object that crosses his visual field.

Mild Dysfunction

- Suspected hearing loss, or
- Suspected vision loss

There is suspicion of hearing or vision loss as evidenced by inconsistent focusing or localization of sound. Responsiveness to touch is not impaired.

Moderate Dysfunction

- Not reactive to auditory stimuli, or
- Not reactive to visual stimuli

There is lack of evidence for hearing or vision as demonstrated by lack of focusing, or localization of sound. Responsiveness to touch is not impaired.

Severe Dysfunction

- Not reactive to auditory stimuli, and
- Not reactive to visual stimuli

There is lack of evidence of hearing or vision as evidenced by lack of tracking, and localization of sound. Responsiveness to touch is not impaired.

Very Severe Dysfunction

- Abnormal response to touch or pain

Infant/child has abnormal response to touch or pain as evidenced by the absence of purposeful, or semi-purposeful movements. There may be a withdrawal or spinal response.

COMMUNICATION**Normal**

- Vocalization appropriate for age, and
- Interactive facial expressions or gestures.

Infants make sounds to make presence known. Children use words to convey needs. Interactive facial expressions and gesture are a process of non-verbal communication, often closely associated with emotions.

Mild Dysfunction

- Diminished vocalization
- Diminished social expression - facial or verbal

There is a decrease in socialization and social expression.

Moderate Dysfunction

- Absence of attention-getting behavior

Infants and children who do not demonstrate behavior that “says” “look at me, here I am”. Children may initiate attention-getting behavior, but cannot communicate their needs.

Severe Dysfunction

- No demonstration of discomfort

Infants and children do not cry or cry very little with painful procedures or if uncomfortable.

Very Severe Dysfunction

- Absence of communication.

There is no communication using facial expressions, body posture, or voice. There is no communication regarding physiological or psychological needs.

MOTOR FUNCTIONING**Voluntary movements: Normal**

- Coordinated body movements, and
- Normal muscle control, and
- Awareness of action

Infants and children have coordinated movements with normal muscle control. They are aware of the action and its purpose (e.g., infant kicks limbs, vocalizes when parent enters.) Infant can hold rattle and transfer it from one hand to another. Toddler carries object, holds onto stuffed animal, sucks thumb. Child writes or plays with toys.

Mild Dysfunction

- 1 limb functionally impaired

There is a partial or complete loss of functionality of the (1) limb. Impairment may be from medical devices such as soft or hard restraints, arm boards for IVs, bandages, casts, or due to physical and medical issues such as deformities, weakness, stiffness, spasticity, and/or movement disorders. Weakness is demonstrated when infants and children are able to move limb off a surface (against gravity) while holding an object or against resistance. They may be able to perform normal age appropriate activities but with increased effort. Stiffness is demonstrated when one or more limbs have increased resistance to passive motion but are still held in normal position or postures. Stimulation does not result in flexion, extension or arching. Spasticity is abnormally increased muscle tone with involuntary movement. Limb(s) feel tight, rigid and limb reflexes are exaggerated. There is resistance to bending and the neck is hyperextended.

Moderate Dysfunction

- 2 or more limbs functionally impaired

There is a partial or complete loss of functionality of 2 or more limbs. Impairment may be from medical devices such as soft or hard restraints, arm boards for IVs, bandages, casts, or due to physical and medical issues such as deformities, weakness, stiffness, spasticity, and/or movement disorders. Weakness is demonstrated when infants and children are able to move limb off a surface (against gravity) while holding an object or against resistance. They may be able to perform normal age appropriate activities but with increased effort. Stiffness is demonstrated when one or more limbs have increased resistance to passive motion but are still held in normal position or postures. Stimulation does not result in flexion, extension or arching. Spasticity is abnormally increased muscle tone with involuntary movement. Limb(s) feel tight, rigid and limb reflexes are exaggerated. There is resistance to bending and the neck is hyperextended.

Severe Dysfunction

- Poor Head Control

Head control is poor with decreased ability to hold head upright at 90°C. Unable or cannot hold head still when less than 90°C. If trunk is supported

head will fall back, to side or front and he/she is unable to bring head to the upright position if sitting or midline if supine or prone.

Very Severe Dysfunction

- Paralyzed
- Decerebrate/Decorticate Posturing

Paralysis is the loss of voluntary motor function. There is abnormal muscle tone. Mental Status may be preserved or altered. Decerebrate posture consists of rigid extension of all extremities with internal rotation. There is downward pointing of toes. Decorticate posture consists of rigid flexion of upper extremities with clenched fists and extension of lower extremities.

FEEDING

Normal

- All food taken PO with age appropriate help.

There is no parenteral or gavage feeding. Feeding methods are age appropriate. Caloric intake is not a classification criterion for this category.

Mild Dysfunction

- NPO, or
- Need for age-inappropriate help with oral feeding

There is no parenteral nutrition or tube feeding. (Dextrose solutions of 5% or less are not considered parenteral nutrition). Examples of age-inappropriate feeding include feeding by a caretaker when independent feeding is expected or when a feeding aid such as a bottle is used at an inappropriate age.

Moderate Dysfunction

- Tube feedings with or without additional oral intake

Tube feedings include nutrition via a nasogastric, oral-gastric, or small bowel tube. There is no parenteral nutrition. (Dextrose solutions of 5% or less are not considered parenteral nutrition).

Severe Dysfunction

- Parenteral nutrition in addition to oral or tube feeding.

Parenteral nutrition includes intravenous nutrition via a peripheral or central vein with a dextrose concentration greater than 5%. It usually includes fat and protein.

Very Severe Dysfunction

- All nutrition is parenteral

Parenteral nutrition includes intravenous nutrition via a peripheral or central vein with a dextrose concentration greater than 5%. It usually includes fat and protein. Child is unable to tolerate *any* enteral feeds, whether by mouth or tube feedings.

RESPIRATORY STATUS**Normal**

- Room air and no artificial support or aids

The infant or child is breathing in room air without the need for artificial help including suctioning, oxygen, or mechanical support.

Mild Dysfunction

- Oxygen, and/or
- Suctioning

Oxygen given via any apparatus including blow-by, cannula, face mask, etc. Suctioning includes any oral or tracheal suctioning.

Moderate Dysfunction

- Tracheostomy

Severe Dysfunction

- CPAP for all or part of the day, and/or
- Mechanical ventilator support for part of the day

CPAP (Continuous positive airway pressure) may be administered through a facemask or tracheostomy. Mechanical support includes positive or negative pressure ventilation devices such as bipap, and positive pressure mechanical ventilation.

Very Severe Dysfunction

- Mechanical ventilatory support for all day and night.

Mechanical support includes positive or negative pressure ventilation devices such as bipap, and positive pressure mechanical ventilation.