Translating an Adult Ventilator Computer Protocol
To Pediatric Critical Care
CPCCRN Protocol Number 011

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child
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PROTOCOL TITLE:

Translating an Adult Ventilator Computer Protocol To Pediatric Critical Care

Short Title: Vent CDS R21
CPCCRN Protocol Number: 011

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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

Acute Hypoxemic Respiratory Failure (AHRF) is severe hypoxemia that is refractory to supplemental oxygen. Primary conditions that underlie AHRF include Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Mechanical ventilation is a primary intervention in nonpremature infants and children with AHRF/ALI/ARDS and serves as the focus of this proposed study. Ventilator management is the accumulation of multiple iterative decisions. This type of decision making can be amenable to guidance using a medical treatment protocol; which facilitates consistent, evidence-based decisions for equivalent patient states. The medical treatment protocol may be implemented within a computer-based decision support tool (CDS).

The overall goal of the proposed research is to investigate the changes related to size and scale (granularity) that are required to modify a ventilator management protocol for AHRF management, developed for adult critical care ("adult protocol"), for pediatric practice. The adult protocol was chosen as the basis for our pediatric protocol because adherence to the adult protocol was high and the findings from the adult study had a profound impact on mechanical ventilation practices in both adult and pediatric ICUs. Although findings from adult research are frequently assumed to apply to the pediatric setting, interventions should be evaluated to ensure that that they reflect unique aspects of pediatric practice, and that the intervention is safe and effective. Preliminary evaluation of the adult protocol suggested that changes related to size and scale (granularity) would be necessary for use in the pediatric ICU. The study is guided by the Unified Theory of Acceptance and Use of Technology (33). Clinician acceptance poses a particular challenge to CDS tool usage. For this study we specifically focus on the modifications to size and scale ("granularity") of the data and recommendations and the influence of those modifications on potential acceptability of the pediatric ventilator protocol. We plan to evaluate ventilator management decisions in the pediatric critical care environment, when decisions are not guided by a computer protocol (social norms); and to evaluate the granularity level at which pediatric critical care providers would accept ventilator management decisions recommended by a protocol (performance expectancy). We have intentionally excluded the implementation of the protocol within CDS software (issues that may affect *effort expectancy*).

This study addresses variability in physician practice across PICUs regarding care of children on ventilators, with the aim of standardizing these practices during the conduct of clinical research that involves mechanical ventilation as either the primary intervention or as a surrogate outcome. Incorporation of CDS as part of a research protocol is an innovative methodology that can support meaningful interventional research studies in critically ill children. Preliminary data from a single institution support the study hypotheses but need to be validated across multiple institutions to determine the feasibility of using a CDS tool to support research projects in the CPCCRN. The study has a multiple PI leadership plan that capitalizes on the complementary skills of the lead PIs; and takes advantage of existing Collaborative Pediatric Critical Care Research Network (CPCCRN) infrastructure. CPCCRN investigators are experienced pediatric intensivists and researchers. Their commitment, large clinical sites and the stable infrastructure of the Network including the CPCCRN Data Coordinating Center, provide a strong environment for this particular study.

STUDY SUMMARY

Specific Aims & Hypotheses

Specific Aim 1: To determine the size and scale of usual care ventilator management practices, not guided by a computer protocol.

We will use a prospective observational study to determine the frequency and scale at which pediatric practitioners make changes in ventilator settings, and patient data that drive those changes, when decision making. We hypothesize that there will be wide variability in usual care practice.

Specific Aim 2: To determine the potential acceptability of recommendations from a computer protocol for ventilator management in the pediatric ICU.

We will use a web-based survey that includes clinical scenarios that simulate interactions with a computer protocol and that highlight key areas where the protocol has been modified. We hypothesize that pediatric intensivists will accept at least 90% of clinical scenario recommendations, and that more granular recommendations (smaller changes) will be accepted at a higher rate than less granular recommendations (larger changes).

Overall objective

The overall objective of this study is to determine the changes to be made to the knowledge base (rules, data, and recommendations) for a CDS tool for mechanical ventilation to be used in a later CPCCRN study.

This study addresses CPCCRN goals. Results from this study will help us to optimize a ventilator management protocol for pediatric patients and will provide preliminary data anticipating compliance with such a protocol in future studies. A protocol that is found to be acceptable and safe for patient management will provide more uniform ventilator practice, and will serve as a sound basis for future rigorous clinical research in pediatric ventilator management and studies in which readiness for ventilator extubation is used as an outcome measure.

Subject Eligibility

Inclusion criteria for patients (aim 1)

- Mechanically ventilated
- Pediatric patients (non-premature newborn to 18 years of age).
- Signs of AHRF: Two consecutive SF O2 ratios < 260 or PF O2 ratios < 300 within 12 hours of start of mechanical ventilation through ETT or tracheotomy.

Exclusion criteria for patients (aim 1)

- Evidence of unrepaired congenital cardiac disease
- Endotracheal tube (ETT) leak >20% (The ETT leak is the difference between inspired and exhaled tidal volume, measured at the endotracheal tube with a pneumotachometer; can also be measured at the ventilator)
- Lack of volume, pressure and flow measurements at the ETT
- Patients receiving ECMO therapy

Inclusion criteria for physicians (aim 2)

ICU physician at CPCCRN centers; who are ventilator management decision makers and who practice primarily in the pediatric ICU (not exclusively cardiac surgery ICU). No exclusion criteria for physicians. The term "physician" in this protocol includes an advanced practice nurse practitioner who serves as an "Attending" at one of the CPCCRN PICUs.

Anticipated Accrual and Study Duration
At all sites: 320 total. There will be a maximum of 120 patients in Specific Aim 1, and up to 200 physicians total in Specific Aim 2.
The estimated duration of the study is two years. This observational study examines up to 7 days of ventilator data for patients. For physicians, participation is via a single point in time survey.

BACKGROUND AND SIGNIFICANCE

Mechanical Ventilation in Pediatric ICU
About 30% of PICU patients are supported by mechanical ventilation(1). However, little is known about how best to ventilate patients with specific conditions(2) such as Acute Hypoxemic Respiratory Failure (AHRF); severe arterial hypoxemia that is refractory to supplemental oxygen. It is caused by intrapulmonary shunting of blood secondary to airspace filling or collapse. Primary conditions that underlie AHRF are Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Ventilator management for ALI and ARDS has been examined in adults (3;4). The paper-based mechanical ventilation protocol used by the adult investigators was based on a computer protocol developed over a decade (5). This ARDSNet protocol is now a widely accepted standard for ventilator management in adult patients with ARDS/ALI.

Small number of patients, low mortality, heterogeneity of disease conditions, variable ventilator management strategies, and poorly defined outcomes make PICU studies difficult (1;6). As a result, many pediatric intensivists extrapolate conclusions from adult studies. Over the past few years most pediatric intensivists have come to target tidal volumes of about 6 mL/kg, based on the adult studies(4). However, the applicability of a low tidal volume strategy in pediatrics has never been formally and rigorously evaluated.

Additionally, factors such as time on the ventilator or readiness for extubation are common surrogate outcome measures in a variety of PICU studies. Without consistent ventilator management, ventilator-related outcome measures are subject to variability between centers and practitioners which can obscure the effect of the intervention being investigated.

Medical Treatment Protocols in Research
In research, the study intervention protocols are expected to be followed unless patient safety issues arise. Many times, the intervention is straightforward, such as administration of a pre-defined dose of a medication. However, some studies in the ICU involve complex interventions (medical treatment protocols), in which the "intervention" is an adjustment of care practices aimed at driving the patient's condition toward some pre-defined target value(9). For example, medications may be titrated to reduce blood pressure, an insulin drip may be given to manage blood glucose, or as in this study, ventilator settings may be adjusted to manage the patient's respiratory status. The "intervention" of interest in the research study is the cumulative effect of a set of multiple adjustments to the patient's care, at multiple points in time. Because each of those adjustments requires the clinician to make a decision, the implementation of the research intervention, then, is subject to clinician decision making biases and variability(9). Such complex research interventions are likely to benefit from decision support, in reducing variability caused by biases and error. However, there is a paucity of evidence-based clinical decision tools to guide PICU practice. Guidelines can be too broad to bring about consistent implementation (7;8). Explicit protocols aim to ensure flexible but consistent, evidence-based clinician decisions for equivalent patient states (9). Such tools have the potential to improve the quality of medical care(10) , reduce errors(11), and improve patient outcomes (12). For example, an anti-infective tool(13) appeared to be beneficial to children and led to cost savings.

Computer Decision Support-an Innovation in PICU Research

It has become imperative that clinicians use information technology. CDS tools offer a method to implement evidence based processes, including complex ICU guidelines(8). Paper-based decision tools can be complex and difficult to follow, leading to low(19) or unknown adherence rates(8), whereas high adherence has been demonstrated with computer-based tools(20;21). Computers support implementation of protocols by standardizing descriptors and procedures, consistently performing calculations, and by capturing relevant data; and can protect users from information overload(9;16;22;23).

A primary mechanism by which computer decision support (CDS) may improve care is through reduction in unnecessary decision variability(9). A significant issue with protocols is **clinician acceptance**(15-18). Acceptance can be supported by developing a protocol that is viewed by clinicians as *reasonable* consensus decisions. An agreed-upon protocol for implementing research interventions may improve consistency and consensus within and between PICUs (14). Compliance with CDS recommendations should not be automatic, however. What computers are not good at is thinking beyond their programming. Aspects of the patient's clinical status could lead the clinician to appropriately reject a computer protocol recommendation(24-26). The goal of CDS tools is not blind acceptance of the protocol, but rather, thoughtful adherence to the extent that is clinically appropriate.

This study is novel by proposing refinement in the methods for conducting clinical studies in the PICU. Most of the prior studies of ICU computer protocols have been in adults, with only a small handful of studies involving children.

CDS Tools for Mechanical Ventilation

Studies in adult ICUs support the benefits of protocol-based ventilator management. Reported benefits included decreased duration and costs of mechanical ventilation and improved collaboration between health care team members. Reports in the PICU have been variable, with one study of protocol-managed ventilator weaning showing reduced time to extubation readiness (29) and another study showing no decrease in weaning time(19). The latter study entailed 2 complex paper-based protocol arms with poor compliance. Both of these studies were limited to the weaning phase alone. In our CPCCRN PICU studies we anticipate needing to manage the entire length of ventilator management after stabilization, not just the weaning phase.

A study that used a protocol for overall ventilator management in addition to weaning found reduced weaning time and time to spontaneous breathing modes but no difference in overall ventilator duration(14).That study used a paper protocol, and the authors note that a limitation was their inability to determine compliance with the protocol. Two other studies used paper protocols. Willson et al. (30) used a paper protocol outlining a broadly defined lung protective strategy. Curley et al (31) used the adult ARDSNet ventilation paper protocol. Neither paper addressed protocol compliance. A pilot study by Jouvet et al. in 2007(32) used a closed loop protocol for mechanical ventilation, but provided no details regarding its claimed derivation from an adult protocol. A closed loop protocol allows no clinician input into the final decision, which may raise safety concerns among clinicians and reduce acceptability for use of the protocol in research.

Adapting Adult Protocols for PICU use

Although it is a reasonably common practice to apply evidence from adult studies to the care of children, little is known about the use in pediatric medicine of CDS tools that were derived from adult tools. While children are developmentally and physiologically not “little adults” (27), it appears that at least some protocols could be used in both adult and pediatric patients.

Appropriate translation from adult practices must be demonstrated rather than presumed. It is unlikely that a ventilator protocol developed in the adult ICU(5) can simply be deployed in the pediatric setting.

The protocol must be shown to be safe, effective, and appropriately sized. Clinicians should be involved in developing and validating CDS content/rules (8;26). In the pediatric population of interest in this study, ventilator strategies are not age specific. However, adult and pediatric practices differ.

Intensivists in the national Collaborative Pediatric Critical Care Research Network (CPCCRN)(28) identified areas in the adult ventilator protocol that were in need of modification to size and scale (granularity) for pediatric use. This study is intended to verify those modifications to size and scale within the ventilator management protocol. It is intentionally focused on the protocol "knowledge" (rules) and does not evaluate the implementation of those rules within a computer decision support system.

This study has potential for substantial impact. Results will help us to optimize a ventilator management protocol for pediatric patients, and will provide preliminary data anticipating compliance with such a protocol in future studies. This study will address CPCCRN goals (28), providing a way to standardize and document ventilator management strategies for studies in which ventilator-related measures are used. The study has the potential to provide valuable information about current ventilator management practices, and could provide insights about evidence based clinical tools, and about clinical research methods and techniques in the PICU.

If the aims are achieved we will have a tool to support clinical trials and comparative effectiveness research within the CPCCRN network and beyond. Additionally, we will have a sound basis for future rigorous clinical research in pediatric ventilator management. We plan to use a computer protocol in a future study, within the NIH R01 or CPCCRN mechanisms. A study of ventilator strategies, well controlled using a computer protocol, has the potential to improve outcomes for children with ALI/ARDS. In addition, a tested, accepted, computer-based protocol for pediatric mechanical ventilation, in and of itself, is likely to decrease variability and improve care for all children requiring such support.

Theoretical Framework

The United Theory of Acceptance and Use of Technology (UTAUT) provides the theoretical framework for the study. The UTAUT (33) integrates elements from eight prominent IT acceptance models, developed from behavioral theories including the theory of reasoned action, diffusion of innovation, and social cognitive theory. The model has been validated and has been shown to explain up to 70% of variation in IT acceptance.

CDS tools consist of delivery mechanisms (software), and content. The content includes the knowledge base (rules), patient data that are associated with specific rules, and recommendations returned to the user. For this study we focus on the framework constructs applicable to the content of a CDS tool, indicated in bold (figure 1), and we excluded the software components, indicated by dashed boxes (figure 1):

- **Use behavior** – actual use of the software. Not directly measured in this study, but in estimates of potential compliance with protocol recommendations.
- **Behavioral intent** – stated intent to use a system. Predicts actual usage of the software. Operationalized in this study as stated intent to follow a computer protocol recommendation (aim 2) and extent to which actual ventilator management practices are in line with what the protocol would have recommended (aim 1).
- **Performance expectancy** – the degree to which a person believes a system will enhance job performance. Includes perceived usefulness, extrinsic motivation, and job fit. This was found

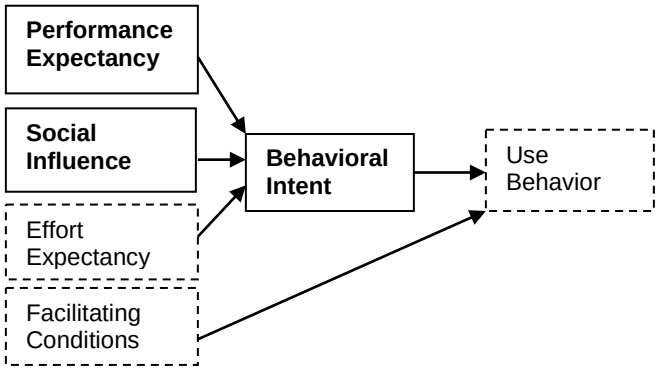

Figure 1. Simplified view of UTAUT model

to be the strongest predictor of behavioral intent in validation studies. Evaluated in aim 2.

- **Social influence** – the degree to which an individual perceives that important others believe he or she should use the IT system. Also called subjective norm or social norm. Evaluated in aim 2; partially evaluated in aim 1 (description of usual care practices)
- **Effort expectancy** – degree of ease associated with the use of a computer system. Not evaluated in this study, because we are not implementing a functional CDS tool as part of the study.
- **Facilitating conditions** – the organizational and technical infrastructure to support use of the system. Not a focus of this study, because we are not implementing a functional CDS tool as part of the study.

Gender, age, experience, and voluntariness are included in the UTAUT model as potential moderators of the four determinants. Factors unique to the system may also be influential (33). We posit that the granularity of pediatric decision making is such a factor. We use the term granularity to include the magnitude and frequency of changes to ventilator settings. Smaller changes equate to "more granular" decisions. The term also includes the size of "bins" into which patient data are grouped to trigger a decision. Granularity may be reflected within usual care practice (social norm) and in perceptions about potential usefulness of a computer protocol (performance expectancy). We acknowledge that pediatric clinicians may be *willing* to accept recommendations for larger changes to ventilator settings than is their usual practice.

PRELIMINARY STUDIES

We have prior experience in adapting research findings and protocols developed in adult ICU for use in the PICU. Studies of a computer protocol for glucose management in the ICU showed that control was tighter for the computer than paper or simple guideline(20). The adult glucose protocol was readily adapted for pediatric use, was well accepted (26;34), and appeared to be as applicable to children as to adults(34). This lends support to development of CDS in other areas such as ventilation.

Both the paper and computer versions of the adult ventilator protocol (4) use grids to categorize patient state relative to a "target zone" for oxygenation and ventilation, and to recommend changes to ventilator settings. Preliminary data suggest that granularity modifications are needed for pediatric use. The adult protocol called for changes to inspired oxygen (FiO2) to be in 0.1 increments or decrements (Figure 2). Our preliminary data (36) suggest that pediatric practice more often involves changes of 0.05. Similarly, the adult protocol used pH ranges to determine changes in ventilator rate and tidal volume. Pediatric intensivists voiced concerns that these ranges may be too broad, and preliminary data support smaller pH range bins in usual care in one site.

Oxygenation (acceptable)

Use when in acceptable range of arterial oxygenation (PaO2 55-61

PEEP	FiO2=0.3	FiO2=0.4	FiO2=0.5	FiO2=0.6	FiO2=0.7
5	Maintain current therapy.	Maintain current therapy.	Increase PEEP by 3	Decrease FiO2 by 0.1. Increase PEEP by 3	Decrease FiO2 by 0.1. Increase PEEP by 3
8	Increase FiO2 by 0.1	Maintain current therapy.	Maintain current therapy.	Increase PEEP by 2	Increase PEEP by 2
10	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1	Maintain current therapy.	Maintain current therapy.	Maintain current therapy.
12	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1	Maintain current therapy.
14	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1. Decrease PEEP by 2	Increase FiO2 by 0.1.	Maintain current therapy.

Figure 2. A portion of an oxygenation decision grid, with changes in 0.1 increments

Timing may also need to be modified. The adult ventilator protocol advocates evaluation for changes in ventilation every 2 hours. While this may speed up the efficiency of the weaning process, it may be out of range with current pediatric practice. Based on single institution data, we expect that pediatric practitioners make changes in ventilation every 4 hours on average. Finally, our data suggest that pediatric practitioners tend not to increase ventilator rate above 25 breaths per minute, likely because of the use of pressure support on other breaths. The adult ventilator protocol, perhaps because of the use of an assist control mode of ventilation, advocates ventilator rates up to 35 breaths per minute.

STUDY DESIGN AND METHODS

This is a descriptive/observational study. Preliminary data guided initial adaptation of the protocol. Prospective observational data from CPCCRN pediatric ICUs will be analyzed to verify that the new, more granular protocol is in line with current pediatric practice, or highlight areas that require further development or refinement (Aim 1). No interventions are involved, and patient care will not be affected by participation in the study. We then use fabricated clinical scenarios delivered via a web-based questionnaire to evaluate potential clinician acceptance at critical points in the translation process (Aim 2).

Specific Aim 1: To determine the size and scale of usual care ventilator management practices, not guided by a computer protocol.

Specific Aim 2: To determine the potential acceptability of recommendations from a computer protocol for ventilator management in the pediatric ICU.

STUDY PROCEDURES

Aim 1Participant Enrollment

Data from mechanically ventilated pediatric patients (non-premature newborn to 18 years of age) will be collected for up to 168 hours (7 days) during their disease onset through weaning phase to extubation or death. Data will be gathered from the 7 CPCCRN sites (8 PICUs – one site has two ICUs). We expect an average of 15 and maximum of 25 patients per site. There are no interventions and no comparison groups and thus no randomization. Sequential patients with AHRF (ALI or ARDS) who meet study criteria will be evaluated over a 12 months period at the CPCCRN sites

Site N patients = 15-20. Total N patients = 120. Expected length of patient participation

- Mean 6 days on ventilator
- Mean 4 observations per day

Aim 1 Data collection:

On enrollment in the study, baseline characteristics of each patient will be noted: diagnosis, age, race, date of birth (DOB), gender, height, weight, ulna length, hemoglobin and CXR report (if films requested for clinical management reasons). Additionally, the patient's vital status (alive or dead) at ICU and Hospital discharge will be collected.

Ventilator data will be collected upon enrollment, at each ventilator change (change to oxygenation (FiO2) or ventilation (PEEP, PIP, tidal volume)), and with each arterial blood gas measurement. Data points include start and stop date and time of mechanical ventilation, make of ventilator and pulse oximeter; mode of ventilation; ETT or tracheotomy leak; inspired O2 concentration; peak, mean and end-expiratory ventilator pressures, rate and tidal volumes and pressure support delivered. The site where tidal volume (VT) measured (i.e., at endotracheal tube, not ventilator) will be recorded each time.

Each arterial blood gas measurement during the time frame of the study will be collected. Pulse oximeter data corresponding in time to ventilator data will be obtained if available.

Data not used to drive ventilator management decisions (such as temperature) are not collected.

Table 1. Data points for Aim 1

Measurement	**Enrollment**	**Each Ventilator Change***	**Each ABG ***
Make of Pulse Oximeter	X		
Make of Ventilator	X		
Mode of Ventilation	X		
ETT or tracheotomy tube leak (%)		X	X
SpO_2 (%)		X	X
PaO_2 (mmHg)		X	X
$PaCO_2$ (mmHg)		X	X
pH		X	X
End-Tidal CO_2 (mmHg)		X	X
Base Deficit (mEq/L)		X	X
FiO_2		X	X
PEEP (cmH_2O)		X	X
Mean Airway Pressure (cmH_2O)		X	X
VT (mL/kg) (at ETT) $^{\Omega}$		X	X
PIP (cmH_2O)		X	X
PS (cmH_2O)		X	X
Ventilator Rate (bpm)		X	X

* Time stamped, to be converted to a time interval for frequency of changes.
$^{\Omega \text{ Site}}$ where VT measured (i.e. at endotracheal tube, not ventilator) will be recorded each time

All CPCCRN sites routinely collect this type of data on patients with ARDS/ALI. They are typically collected on a ventilator log form. In addition, all CPCCRN sites have ventilators capable of storing all relevant ventilator data relating to time, pressure, volume and flow on PCMCIA cards and exportable to spreadsheets. Some CPCCRN sites can also download this data directly from the ventilator, and/or from an electronic medical record (Newth, unpublished CPCCRN survey, 2010). The data to be collected is objective and inter-rater reliability testing will not be necessary. Data collectors will be trained at a scheduled (quarterly) CPCCRN Steering Committee meeting. The PIs will work directly with study coordinators from each CPCCRN site to evaluate data collector capability & training needs.

<u>Aim 2 Participant Enrollment</u>
Surveying health care providers about their practices and perspectives is vital because providers play a central role in implementing guidelines, standards of care, and technologies. In order to maximize response rate, we will use a modified Dillman approach (37), also known as modified Tailored Design Method (38) for survey logistics. These approaches are considered the standard implementation method for survey research. While a response rate of about 50% has historically been considered acceptable in surveys of professionals such as physicians (38, 39), the Dillman approach and similar methods have resulted in higher response rates (38). The approach includes: respondent-friendly questionnaire design; multiple contacts with personalized correspondence; tracking the delivery of survey invitations; and methods that convey respect for the respondents' time such as first class stamps on paper correspondence and a gift certificate or monetary token of appreciation. Endorsement of the survey by a colleague or a

professional association has also been shown to improve response rates (39). Because this is a web-based survey we have modified the approach to use both paper and electronic communications.

Each site will send a list of PICU Attendings and fellows to the Data Coordinating Center at the University of Utah (DCC). The DCC will assist with managing contacts, personalizing correspondence, and tracking response rates; and will ensure that survey responses are anonymized prior to analysis.

For this study we will use the following contacts:

1. Pre-notice: a paper letter notifying physicians of the upcoming survey; followed by an email from the site Research Coordinator, also notifying of the upcoming survey and includes the Survey Cover Letter.
2. Invitation to participate and survey cover letter: an email invitation with a link to the survey.
3. A thank you/reminder notice sent to all participants via email.
4. Up to 2 additional reminders sent via email to non-respondents
5. A final paper letter thanking respondents for participating and containing a token of appreciation.

If potential respondents indicate they do not agree to participate (on the first page of the survey) they will not receive further reminders.

Table 2. Summary of survey communications

Mixed Mode Survey Logistics				
Contact	**Time**	**Mode**	**From**	**To**
1a. Pre-Notice	T	Paper	Sward & Newth	All potential invited participants
1b. Pre-Notice & Survey Cover Letter	T+3 days	Email	Site RC	All potential invited participants
2. Survey Invitation	T+1 week	Email	Sward & Newth (Survey Software)	All potential invited participants
3. Thank you or Reminder	T+2 weeks	Email	Sward & Newth (Survey Software)	All potential respondents
4a. Reminder	T+4 weeks	Email	Sward & Newth (Survey Software)	Only those who have not completed survey
4b. Reminder	T+~6 weeks	Email	Sward & Newth (Survey Software)	Only those who have not completed survey
5. Thank you and Token of Appreciation	T+~8 weeks	Paper	Sward & Newth	Everybody who completed the survey

Aim 2 Data Collection

Aim 2 will collect data via a web based questionnaire that examines behavioral intent (intent to accept or decline protocol recommendations) and performance expectancy (perceptions about the usefulness of recommendations) through scenarios. We will present fabricated ventilator decision input data and resulting computer protocol recommendations. The user will be asked if they would accept or decline the recommendation, and if declining, the reason for it. Additional items evaluate potential demographic moderators and indirect influences such as attitudes and self-efficacy.

Survey Development: Clinical scenarios will be developed around “critical points” which differ between the pediatric and adult protocols in areas of high, medium and low oxygenation, as well as increases and decreases in ventilation. Questions will be structured to reflect both the adult and pediatric protocol levels of granularity. Additional scenarios will be developed to explore areas potentially in need of revision, as revealed through analysis of aim 1 data. The questionnaire will be examined for face validity and

adequacy of sampling ("Are all the key areas which differ between the adult and pediatric protocol represented?").

A panel of 3-5 MD volunteers who are experienced in the management of mechanical ventilation for pediatric patients will pilot test the survey and provide additional evaluation of whether the items appear representative, whether construction of items is reasonable (i.e., the wording and presentation of scenarios), and any issues with the web-based survey instrument. We will use a secure web based tool such as CheckBox (www.checkbox.com) to deliver the questionnaire.

Because the survey development is part of this aim, the finalized questionnaire will be submitted to site IRBs as an amendment. See appendix for survey questions.

No patient data will be involved in the questionnaire – all scenarios are fabricated.

Data Points for survey:

- Accept/decline indication for each scenario
- Reasons for declining recommendations
- Participant demographic data
- Selected items from UTAUT model (33), modified to represent content within the proposed computer protocol.
- Specific questions regarding ventilator management practices

Survey responses will be anonymous and users may omit any item they do not wish to answer. The survey software supports confidentiality and allows user anonymity. No personal health information (PHI) will be collected and only minimal demographic data. Names and contact information, required for invitations to participate and for tracking of monetary tokens of appreciation, will be separated from the survey results by the University of Utah Data Coordinating Center staff prior to data analysis.

ANALYSIS PLANS AND SAMPLE SIZE DETERMINATION

Aim 1 Analysis Plan

The primary analyses will use data from patients who had at least one arterial or capillary blood gas measurement. We will use graphical summaries (e.g., histograms, boxplots) to examine the distributions of the size and frequency of changes. Based on the shape of each distribution, descriptive statistics will also be used to further assess clinical decisions. In particular, we will assess the average (median, mean), variability (standard deviation, quartiles) and range (minimum and maximum values) for incremental changes in FiO2, PEEP, PIP, and tidal volume (VT). We will calculate two-sided 95% confidence intervals (estimate ± margin of error) for the mean, or in the case of skewed distributions, the median.

We may evaluate the association between these parameters and other available clinical characteristics. For example, the frequency and extent to which changes are made based on non-invasive (e.g. pulse oximeter) versus invasive (e.g. arterial) blood gas information will be examined. We will assess the variability of practice and the maximum and minimum limits accepted for incremental changes in FiO2, pH, PEEP, tidal volume and PIP. These analyses would clearly be exploratory, with the purpose of informing further development or refinement of the decision support tool. No formal adjustment for multiple comparisons will be made. These calculations will incorporate clustering at the patient and site level. For example, the mean value and 95% confidence interval for a continuous measure with patient- and site-level clustering can be estimated using an intercept-only generalized estimating equations (GEE) model.

The adult ventilator protocol advocates evaluation for changes in ventilation every 2 hours. While this may speed up the efficiency of the weaning process, it may be significantly out of range with current pediatric practice. Based on single institution data, we hypothesize that pediatric practitioners make changes in ventilation every 4 hours on average. We will test if this holds true for ventilator changes across sites by evaluating whether the mean time between changes is different than the 4 hours currently recommended in the pediatric protocol.

For oxygenation changes, the pediatric protocol advocates changes at an interval of 0.05, and we seek to test if this is true at the pediatric institutions participating in Aim 1, by evaluating whether the median change in FiO2 is different than the 0.05 changes advocated in the pediatric protocol. A median change of 0.1 (advocated in the adult protocol) would be considered significantly different.

The tidal volume target is set at 6 mL/kg in the pediatric protocol, measured at the endotracheal tube with a proximal flow sensor. We seek to evaluate whether the mean pediatric tidal volume across institutions falls within the range of 5-7 mL/kg.

Finally, the adult ventilator protocol, likely because of the use of an assist control mode of ventilation, will advocate increasing ventilator rate to 35 breaths per minute (bpm). Data suggests that pediatric practitioners tend not to increase ventilator rates above 25 bpm, likely because of the use of pressure support on other breaths. We seek to test whether this holds across institutions, and if the mean rate, particularly in the low pH range is closer to 25 rather than 35 breaths per minute.

Since the purpose of this aim is refinement of the decision support protocol rather than rigorous hypothesis testing, we would propose no adjustment for the multiple (four) statistical comparisons outlined in the table below. However, even if adjusted for multiple comparisons, our anticipated enrollment (120 patients) should guarantee adequate power. The “N” presented in the table below is the number of patients needed, not the number of observations available. Multiple measurements will be gathered for each patient, providing even more information for both descriptive and inferential measures. Any formal statistical testing based on individual observations will use methods that account for the correlation between repeated measures on the same patient, e.g., Generalized Estimating Equations (GEE).

We will also be evaluating whether the granularity of the pH bins in the current pediatric decision support protocol is in line with current practice. The pH measurements will be plotted against Ventilation Index (VI – a computed measure of change in ventilator support), stratified into the pH ranges advocated by the adult and pediatric protocols. In each of these stratifications, a model will be built to examine the relationship between pH and change in Ventilation Index (pre- and post- ventilator change). If the slope of the regression line is significantly different from zero in any of the protocol bins, it would indicate that practitioners behave differently than the protocol within the aforementioned pH bin. In addition to examining statistical significance, the practical and clinical relevance of any observed relationship within a given pH bin will also be considered.

Aim 1 Sample Size Determination

Preliminary data from a single CPCCRN site using 192 patients with Acute Lung Injury has been used to evaluate assumptions of the developed pediatric ventilator management protocol, and get estimates of variability. The specific areas which differ between the adult and pediatric protocols include frequency of reevaluation (and ventilator changes), granularity of changes in FiO2, granularity of pH bins for ventilation, target for tidal volume, and target for ventilator rate. Our goal is to understand current practice at participating CPCCRN institutions, and determine whether recommendations from the pediatric ventilator protocol fall within “normal” practice at these institutions.

Table 3. Sample size determination for aim 1

Parameter	**Population Mean**	**Population St Dev**	**Alternative Hypothesis**	**Power**	**N**	**N adjusted for multiple comparisons**
Frequency of Change (hrs)	4	1.7	3 or 5	0.8	25	36
FiO2 Change	0.05	0.12	0.1	0.8	55 *	79 *
VT (tidal volume)	6	2.5	5 or 7	0.8	52	73
Vent Rate	25	10	35	0.8	10	15

*Adjusted for non-parametric Mann-Whitney U test using conservative assumptions about the outcome distribution (divided by 0.864).

We expect to collect data on 120 patients yielding an estimated 2,880 observations. Because the primary purpose of this aim is descriptive, the appropriateness of the sample size was evaluated based on the margin of error achieved for a two-sided, 95% confidence interval around the observed mean value. The margins of error were conservatively based on number of patients even though individual measurements will be available for each patient. We also evaluated statistical power for the hypothesis testing described above for pH bin sizes. If we accept that a squared correlation coefficient < 0.15 is not significantly different than zero, and given the expectation of 7 comparisons, we would need 80 observations in each pH range to achieve a power of 90%. Preliminary data showed about 7% of observations fall in the smallest pH range of <7.15. One can extrapolate that approximately 1,200 observations will be needed to obtain 80 in the pH <7.15 range. Therefore, our projected sample size of 120 patients and 2,880 observations will be more than adequate to ensure adequate power for the pH bin analysis component of this aim.

Aim 2 Analysis Plan

The primary analysis for aim 2 is descriptive. To evaluate protocol acceptance (Yes/No), we will use a McNemar's test of proportions. In addition we will evaluate the difference between acceptance of recommendations at two levels of granularity (original and modified protocols). This will validate the need perceived by earlier reviewers for a more granular protocol. Since each physician will respond to multiple paired scenarios, the overall analysis will account for both physician-level and site-level clustering. To examine reasons for declining recommendations we will conduct a content analysis of free text responses.

Aim 2 Sample size determination

Based on anticipated response rates and an anticipated 20% difference between acceptance rates for the protocol granularity levels, 95 survey participants would be needed for a power of 0.8 at an alpha of 0.05. We hope to collect at least 95-110 surveys (to allow for potentially incomplete responses). Given that there are 8 participating CPCCRN PICUs, with a total of just under 200 Attendings and fellows; then the sample size could be attained with less than 55% response rate. In a recent (as yet unpublished) study on physician issues related to death in the PICU, CPCCRN physicians at 7 PICUs had a 59% response rate

(70 MDs) [personal communication, K. Meert, MD, Principal Investigator, Bereavement Study]. Should the response rate be lower than anticipated, it is possible that the survey could be sent to members of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network, a larger network of PICU investigators. Should it become necessary to expand the survey beyond the CPCCRN network, an amendment will be submitted to the IRB.

DATA SECURITY AND CONFIDENTIALITY

As date of birth is typically noted as identifiable information, extensive precautions will be used to maintain subject confidentiality. Each subject will be assigned a unique identifier by the electronic data capture (EDC) system. It will only be possible for the Clinical Center to map this identifier to the subject's medical record number. No direct subject identifiers will be captured by the EDC or stored at the DCC. Staff at the DCC will not be able to determine the identity of any subject enrolled in this study.

The following data access and security methods will be used to transmit, manage and store the data at the DCC:

1. EDC and other web systems, features 128-bit SSL data encryption to ensure data security over the Internet.
2. Systems and databases have access restrictions by Site, Role & User levels with audit trails.
3. Hourly incremental backups and full daily backups provide a high level of protection against data loss.
4. All personnel at the DCC receive training and have signed privacy and confidentiality agreements.
5. Precautions are used to ensure privacy and maintain confidentiality of the information.

The DCC at the University of Utah has a dedicated locked, server room within its offices, and the building has 24 hour on-site security guards. The DCC has a state-of-the art computer infrastructure and 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 three high-speed switches and two hubs. 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. All web applications, including electronic data capturing systems (EDC) use the SSL protocol to transmit data securely over the Internet.

Direct access to DCC computers is only available while physically located inside DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. 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 6 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. 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.

The investigators and staff of the DCC are fully committed to the security, privacy and confidentiality of all data collected. All personnel at the DCC at the University of Utah have signed confidentiality agreements concerning all the data encountered in the Center. In addition, precautions to ensure privacy and confidentiality are put in place for projects. Violation of these agreements may result in termination from employment at the University of Utah. All personnel involved with DCC data systems also received Human Subjects Protection and HIPAA education.

ADMINISTRATIVE RESPONSIBILITIES

The primary center is Children's Hospital Los Angles and the performance sites are the members of the Collaborative Pediatric Critical Care Network. The University of Utah serves as the data coordinating center for this study, as it does for other CPCCRN studies.

This study is funded by NICHD as a multiple-PI study. A Multiple-PI leadership plan is in place (see appendix 2). Dr Newth and CHLA are the contact PI/primary grant site. Dr. Newth and CHLA staff will coordinate management and communication among sites of information obtained in this research that may be relevant to the protection of research participants, such as:

- Unanticipated problems involving risks to participants or others
- Interim results
- Protocol modifications

Study Resources:
Each of the performance sites for this study has adequate research staffing and clinical staffing to conduct the study. The study will be conducted under the auspices of the Collaborative Pediatric Critical Care Research Network and will utilize its existing research infrastructure. Though this study may impact the workload of the clinical staff, it is believed that it will be minimal and the clinical staff can accommodate this within the patient care environment. The study does require financial support for the additional research staffing time which is included in the budget. IT services are sufficient at each site to support communication with the PIs and the Data Coordinating Center for this study.

The CPCCRN Data Coordinating Center at the University of Utah Data (DCC) will provide statistical and data management support for this study within the Collaborative Pediatric Critical Care Research Network infrastructure. The performance sites, being members of the Collaborative Pediatric Critical Care Research Network already have an established relationship with the DCC and all necessary regulatory relationships are in place. This study will take advantage of established mechanisms of communication and collaboration within the CPCCRN network. In addition, Dr. Sward has access to the University of Utah College of Nursing, Emma Eccles Jones Nursing Research Center which includes: research support staff, statisticians, programmers, grants management, and administrative staff; 22 workstations; 2 interview rooms; and small and large conference rooms equipped with the latest technology including teleconferencing and videoconferencing facilities.

Clinical: Children's Hospital Los Angeles and the other performance sites have excellent facilities with which to conduct the study. All are top flight pediatric intensive care facilities that cater to the care of patients that are the subjects of the study. Existing PICU environments are adequate for this study.

Computer: All key personnel have individual offices with computers equipped with software for data collection and analysis. All computers can access their organization's networks, permitting use of electronic journals and locally-licensed software. Extensive computing facilities are available through the CPCCRN Data Coordinating Center to support this project, including:
1. Hardware/Data storage: 17 servers with storage in excess of 1.2 terabytes. Dedicated locked server room with fire suppression, cooling, uninterruptible power supply. Servers are backed up through a dedicated backup server connecting across an internal gigabyte network to a robotic tape drive, with incremental backups made hourly.
2. Information security: The DCC is housed in a secure building with 24 hour on-site security guards. Direct access to DCC machines is available only while physically located inside the DCC offices, or via a VPN client. The network infrastructure and security are coordinated 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.
3. Network communications: Communication over the network is encrypted using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. Secure clinical trials management software (OpenClinica) and eRoom™ is used for data management and communications about Network studies. The eRoom™ is used as a "digital office" to support secure, confidential communication and collaboration among multiple users across the United States. In addition to supporting CPCCRN network communications, it is used as a secure method for implementation of individual research projects.
4. Software resources: In addition to trials management and network communications software, the DCC maintains web server software, robust database software, a Query Management System, statistical software, web conferencing software, and software for development and validation of computer decision support tools.

Office Space: All key personnel have adequate-sized individual offices with locking doors. Dr Newth is located at the Children's Hospital Los Angeles. Dr Sward has adequate office space at the University of Utah Health Sciences Education Building, a $ million state-of-the-art building that is the centerpiece of the academic programs at the University of Utah Health Sciences Center including its nationally ranked medical, nursing, pharmacy, and health training programs. Dr. Sward's office is about 5 minutes from the CPCCRN Data Coordinating Center (DCC) offices.

Participating Sites CPCCRN network sites (and site investigators) are:

- Children's Hospital of Los Angeles (Newth, lead site for this study)
- Children's Hospital of Michigan (Meert)
- Children's Hospital of Philadelphia (Berg)
- Children's National Medical Center (Wessel)
- Mattel Children's Hospital at UCLA (Harrison)
- Phoenix Children's Hospital (Pollack)
- University of Michigan Medical Center (Shanley)
- University of Pittsburgh Medical Center (Carcillo)

IRB approval will be obtained from each site before the site participates in the study.

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