

Evaluating processes of care & the outcomes of children in hospital (EPOCH): a cluster randomized trial of the Bedside Paediatric Early Warning System

Protocol Summary

Background: The ideal outcome of hospitalization is survival with preserved neurologic function. Late detection of clinical deterioration in hospitalized children results in near and actual cardiopulmonary arrest and necessitates urgent ICU admission. We developed a documentation-based system of care to identify children at risk to the healthcare team to prevent these crises. We called it the Bedside Paediatric Early Warning System (Bedside-PEWS). While promising, the effect on important clinical outcomes is unknown.

Work to date: The following are the prerequisite achievements for this trial. [1] Single-centre validation of the Bedside-PEWS score (*completed*). This expert-derived, statistically developed, clinically validated 7-item severity of illness score is superior to the retrospective opinion of nurses and identified 82% of children with evolving critical illness with at least 1 hours notice (AUCROC 0.91). [2] Multi-centre validation (*manuscript under review*). This evaluation (2074 patients, 4 hospitals) confirms good performance of the Bedside-PEWS score in each hospital, in children of all ages, and in different disease populations (AUCROC 0.87). [3] Development of score-matched care recommendations to ensure appropriate matching of the care provided with that indicated by the child's severity of illness (*completed*). [4] Development of the Bedside-PEWS documentation record (*completed*). Score calculation is reliable (ICC 0.92), and nurses say it is both useful and easy to use. [5] Development of Education programs (*completed*). The Frontline Staff Education program and the Bedside-PEWS Instructor course support clinical implementation. [6] Pilot clinical evaluation (*completed*). A single site study found reduced late detection of critical illness, fewer 'stat calls', improved interdisciplinary communication and established safety and acceptability (*Accepted J. Pediatrics & Child Health*).

Objectives: To evaluate the impact of Bedside-PEWS on early identification of children at risk for near and actual cardiopulmonary arrest, hospital mortality, processes of care and PICU resource utilization.

Hypothesis: That the Bedside-PEWS reduces late detection of critical illness, reduces mortality and improves processes of care and does not increase healthcare resource utilization.

Study Design: A multi-centre cluster randomized trial will be performed in 22 hospitals that care for >200 inpatients (<18 years and >37 weeks gestational age) each year and have a PICU. Balanced randomization at hospital level will be achieved by 1:1 allocation in hospitals ≥ 200 and <200 beds.

Intervention: Bedside-PEWS. The documentation record for children cared for in hospital wards (*not OR, not ICU*) will become the Bedside-PEWS documentation record. This has score calculation embedded into vital sign documentation, and specific care recommendations. Control hospitals will continue standard care.

Primary Outcome: All cause hospital mortality. *Secondary Outcomes:* Significant Clinical Deterioration Events, this composite outcome describes the treatment provided before transfer and immediately after urgent PICU admission, or death before PICU admission. It is modified from the 'MERIT' cluster RCT of medical emergency teams in adult hospitals. Eight other clinical outcomes will be evaluated: [1] resuscitation treatments provided before PICU admission; [2] Potentially Preventable Cardiac Arrest. [3] Unplanned hospital re-admission. In patients urgently admitted to PICU [4] severity of illness at PICU admission, [5] organ dysfunction, [6] ICU-mortality, [7] mechanical ventilation and [8] unplanned PICU readmission within 48 hours of PICU discharge. The 5 process of care outcomes are: stat calls, resuscitation calls, ICU or MET-CCRT consultations, frequency of documentation, and staff perceptions. Resource utilization outcomes will be ICU technology use and length of stay (*ICU, Hospital*). Outcomes will be measured prospectively for 18 months (*6 months baseline, 12 months intervention*). A sample of 22 hospitals will permit evaluation of an absolute risk reduction of 0.9 deaths/1000 hospital admissions equal to a relative risk reduction of 18% (k 0.15, power 0.8, alpha 0.05, baseline event rate 5.1/1000).

Analysis: Regression analyses with adjustment for baseline event rates will be used to evaluate the impact of Bedside PEWS on mortality (logistic) and significant clinical deterioration events (Poisson).

Potential impact: If effective, integrating the Bedside-PEWS into routine care will improve survival, reduce morbidity and improve hospital efficiency. If not effective then decision-makers can choose to allocate resources to more effective mechanisms to improve the outcomes of hospital care.

OVERVIEW

The primary objective of hospital-based care is survival with preservation of neurologic function. Late detection of clinical deterioration in hospitalized patients results in near or actual cardiopulmonary arrest and necessitates urgent ICU admission. We have shown that despite apparently successful resuscitation, in-hospital cardiac arrest is associated with significant mortality and acquired morbidity in survivors, and that urgent ICU admission is associated with reduced quality of life and reduced neuro-cognitive functioning.¹⁻⁵

Avoiding patient-care crises is a patient safety imperative that is contingent upon the timely identification, referral and treatment of children whose conditions are clinically deteriorating.^{6,7} Hospitals are currently implementing medical emergency or rapid response teams (MET-RRT) with 'calling' criteria that unfortunately fail to identify many of these children (Table 1).

The Bedside Paediatric Early Warning System (Bedside PEWS) is a scientifically developed documentation-based system of care designed to identify children who are clinically deteriorating while admitted to hospital inpatient wards. It was developed and validated by the applicants.⁸ We have preliminary data demonstrating that the Bedside PEWS addresses multiple factors (communication, hierarchy, secondary review) contributing to delayed treatment of children at risk. In our pilot study of implementation at a single site we showed statistically significant reductions in late transfers, 'stat' calls, decreased apprehension when nurses called physicians to review patients, and improved communication. Our preliminary data show that the Bedside PEWS score is superior to other methods being used to identify children at risk for impending cardiopulmonary arrest. The current application is to support the culmination of this program of research: the definitive trial of Bedside PEWS. A 2-year cluster-randomized trial will evaluate the impact of Bedside PEWS on clinical outcomes, processes of care and resource utilization in 22 paediatric hospitals.

1. The Need for a Trial

1.1 What is the problem to be addressed? Preventable mortality and morbidity. Cardiopulmonary arrest is the final common pathway of different disease processes, each culminating in loss of cardiac output. Treatment of cardiopulmonary arrest represents the most extreme form of 'rescue' from failing -or failed- therapy and was used as one of the sentinel event markers in the 6 largest evaluations of patient safety.⁹⁻¹⁴ Cardiopulmonary arrest occurs in 0.1-20/1000 children in hospital wards.^{2,15-17} Hospital survival is 30-50%,^{1,18,19} and survivors risk significant acquired morbidity.^{2,4,18,20-23} Prevention of cardiopulmonary arrest in hospitalized children is a patient safety imperative. As a manifestation of hospital-system failure, the late identification of patients with evolving critical illness requires a system-level solution. Critical care experts have suggested that the greatest improvements in care will be from system-level interventions rather than single therapies.²⁴ Candidate interventions will need to be effective 24/7 to address the inferior outcomes of patients who are admitted to hospital,²⁵ are transferred from ICU,²⁶ or receive cardiopulmonary resuscitation²⁷ after 'regular-hours'. The feasibility of preventing near and actual cardiopulmonary arrest in hospitalized children is suggested by the experience of many frontline practitioners,^{28,29} and studies reporting that up to 80% of adult cardiopulmonary arrests are retrospectively identifiable.³⁰⁻³⁴ Our data shows that [1] nearly 5000 near and actual cardiopulmonary arrests ('code-blue' events) occur each year in children cared for in the inpatient wards of Canadian and American paediatric hospitals.⁷ [2] Mortality following code-blue events is 28% versus 14% in children urgently admitted to ICU before a 'code blue' call is necessary.³⁵ [3] More than 80% of children at risk could be prospectively identified with at least one hour's notice using the Bedside PEWS score,^{8,15} [4] imperfect communication and hierarchical processes delay referral to available expertise (*revision submitted*). Taken together these data suggest that, if successful, the Bedside PEWS could save the lives of over 500 hospitalized children each year in Canada and the United States.

Cardiopulmonary arrest, near arrest, and organ dysfunction are intermediary morbidity events in hospitalized children. They are precursors to mortality and persisting morbidity manifest as neuro-cognitive injury and reduced quality of life (*Figure 1*).^{1,3,4,23,36-38}

Modern critical care is founded on the principle that the timely provision of optimal treatments improves mortality and morbidity.³⁹ Operationalizing this principle requires timely consultation and engagement of local

expertise (*frontline and supervising nurses, respiratory therapists and physicians*), and timely transfer into a PICU. Improvement in these care processes is likely to improve outcomes of hospitalized children. This provides a rationale for studying early identification of critical illness in hospitalized children rather than cardiopulmonary arrest in isolation.

Mortality in hospitalized children is the consequence of failed or ineffective treatment – either of the primary disease or of the related cardiopulmonary arrest or a combination of both. Hospital mortality is a useful measure of quality of care, is used extensively to benchmark the performance of PICUs,⁴⁰⁻⁴⁴ surgical programs and hospitals,^{45, 46, 47} and will be the primary outcome of this study.

Quality of care and adverse event prevention: the path to improvement. If near and actual cardiopulmonary arrest in patients cared for in inpatient wards is to be effectively prevented then the following must occur: [1] Identification of the patient with evolving critical illness. We have shown this is possible with the Bedside PEWS Score.⁸ [2] Timely referral - well before impending cardiopulmonary arrest. This is the purpose of the score-matched care recommendations of the Bedside PEWS. [3] An early intervention mechanism to respond to referrals, including frontline staff, MET-RRT or other ICU consultation and [4] appropriate areas to provide definitive care.⁷

Current 'solutions' to improve outcomes of hospitalized children with evolving critical illness

The majority of research and administrative efforts to date have focused on finding better treatments (hypothermia, quality of CPR, neuro-critical care, transfusion strategies, extra-corporeal membrane oxygenator ECMO therapy, others), improving physical capacity (more ICU beds, larger hospitals) and facilitating better trained healthcare professionals (simulation, other forms of education) in order to identify and treat patients with evolving and established critical illness.^{1, 3, 48-59} The single and multi-center resuscitation research projects of the steering committee have resulted in publications in journals including JAMA^{1, 27, 60, 61} NEJM,^{48, 49, 52, 58} Circulation,^{3, 62-66} Critical Care Medicine,^{4, 54, 67} Lancet³⁶ and Pediatrics.^{2, 7, 37, 68-72} Despite these efforts, the problem – and consequences of - late detection of critical illness persist.

Medical Emergency Teams (MET)/Rapid Response Teams (RRT) provide rapid access to ICU expertise with the intent of improving patient outcomes.^{73, 74} A MET-RRT 'call' is analogous to an ICU consultation in hospitals without a MET-RRT. As the effectors of expertise, the impact of the MET-RRT (or other ICU team) is dependent upon appropriate identification of patients at risk, and timely referral. Following several positive⁷⁵⁻⁷⁷ and negative⁷⁸⁻⁸¹ studies of MET-RRT in adult hospitals, a multi-centre, cluster randomized clinical trial was performed. The primary outcome was a composite of unexpected death, unplanned ICU admission and cardiac arrest. The MET-RRT used un-validated calling criteria and studied 120,000 adult patients in 23 hospitals. The trial was negative,⁸² but provides several important lessons: [1] Calling criteria were met in <50% of patients with urgent ICU admission – suggesting that the criteria did not identify patients at risk. [2] The number of patients with 'no-event' who met one or more of these calling criteria is unknown. This number is also unknown for the 'criteria' used in the paediatric MET-RRT studies.⁸³⁻⁸⁷ [3] ~90% of the patients who met criteria were referred to ICU teams. This occurred in both MET and control hospitals, suggesting that the calling criteria added little to the expert model. [4] Rates of the composite outcome fell between the baseline period of observation and the intervention period in both intervention and control hospitals – suggesting a study effect, and underscoring the importance of baseline event rates. For this reason we will evaluate baseline event rates in intervention and control hospitals. The other cluster randomized study of the MET-RRT used the Patient-At-Risk score. Sixteen wards in an 800-bed adult hospital were randomized over 32 weeks. In this single centre, short-duration study, the MET-RRT was associated with reduced mortality OR 0.52 (95%CI 0.32-0.85).⁸⁸

There have been five published studies of the introduction of MET-RRT for children.⁸³⁻⁸⁷ All are single center before and after studies, and variably show reduced rates of code-blue calls,⁸³ respiratory arrests⁸⁵ and cardiac arrests⁸⁴ or no change.⁸⁷ The two studies showing reduced all-cause hospital mortality were performed over 6 years⁸⁴ and 7½ years⁸⁶ undermining their ability to describe more than time-related improvement in mortality paralleling population trends.⁸⁹

The Paediatric Critical Care Response Team Collaborative in Ontario (Site leaders: *Kotsakis, Gilleland, Lobos, Morrison*) involves four paediatric referral hospitals. Preliminary evaluation of a 4 year before and after study of the introduction of RRT using the Melbourne calling criteria⁸⁶ was associated with reductions in mortality following urgent ICU admission and code-blue calls, with an average of 6 consultations per week in each site. These data suggest that the “easier access to ICU expertise” with MET-RRT teams may be associated with improved outcomes, however identification to these ICU teams remains problematic.

Identifying patients-at-risk of near & actual cardiopulmonary arrest is the essential prerequisite. The properties of identification methods have not been adequately considered in previous studies of MET-RRT response mechanisms⁸³⁻⁸⁷ There are 7 published paediatric severity of illness scores and calling criteria that quantify severity of illness and use a threshold ‘score’ for ICU referral and or other responses (Table 1).^{15, 17, 83, 85, 90-92} The development of most methods has been methodologically limited, (no control group, use of data from very near the time of the cardiac arrest, no modification of items based on statistical analysis of their performance, use of highly subjective criteria) in comparison with our work.^{8, 15}

There are 4 published **calling criteria methods**, from Melbourne,¹⁷ Bristol,⁹² Cincinnati,⁸³ and Baltimore.⁸⁵ The Cincinnati criteria are subjective, and are no longer used at that hospital.^{83, 93} The Baltimore criteria are subjective and/or triggered by acute medical diagnoses. The authors write “...having a validated system of triggers will be an invaluable component of a reliable PMET”.⁸⁵ The Bristol tool uses a thresholds for airway (nebulized epinephrine, ‘tiring’), breathing (respiratory rate > threshold, apnoea with bradycardia), circulation (blood pressure <threshold, prolonged capillary refill time), and disability.⁹²

The Melbourne Criteria were developed from expert opinion. They include cardiac and respiratory arrest amongst other ‘pre-arrest’ criteria and ‘concern’. Despite increasing use, the ability of these criteria to distinguish sick from well patients has not been well evaluated. Data from their 2009 publication indicates that the Melbourne criteria identified 10 of 24 (42%) patients who had cardiac arrests in their hospital.⁸⁶ In Ontario paediatric hospitals we found that with the use of the Melbourne criteria, 40% of 150 code blue events had preceding MET-RRT activations (*Kotsakis, Co-I*).

There are 4 published **paediatric scores**, including the Bedside-PEWS Score. They are from Brighton,⁹⁰ Toronto (2),^{8, 15} and Cardiff.⁹¹ The Brighton score uses behaviour, circulatory (*colour, relative tachycardia*) and respiratory (*relative increase*) domains, and ‘persistent vomiting following surgery’ with a range of 0 –11.⁹⁰ Subsequent evaluation of this score in a cohort of 2979 children in Cincinnati Children’s Hospital reported 51 PICU transfer events and found an area under the receiver operating characteristics curve of 0.89, with sensitivity of 78% and specificity of 82% at a threshold score of 5.⁹³

In the development cohort, the Cardiff and Vale score had an area under the receiver operating characteristics curve of 0.86, with a sensitivity 69% and specificity 90% at a threshold score of 2. Inspection of the score reveals that children in the first months of life may be expected to routinely score at or above the threshold (2 points for systolic blood pressure <70 mmHg, and respiratory rate >50 breaths / min). The authors state: “Further validation studies are required to find the optimum trigger criteria, intra-observer reliability and completeness of documentation for the different components of these scores”.⁹¹

Our original PEWS Score included 16 items. The score performed well (AUCROC 0.91; sensitivity 78%, specificity 95% at threshold score of 5),¹⁵ but its complexity was prohibitive.⁹⁴ Consequently, we developed the simpler and equally discriminatory, 7-item Bedside-PEWS score.⁸

Preliminary work by applicants: Bedside Paediatric Early Warning System

The Bedside Paediatric Early Warning System is a documentation-based system of care for hospitalized children. There are 4 elements to the Bedside PEWS (*Figure 2*). [1] The Bedside PEWS score is an expert-derived severity of illness score used to quantify severity of illness in children across a range of scores from 0-26. Using a frequency matched case-control design we found the score was able to differentiate between children who were urgently admitted to ICU from ‘well’ hospitalized children, with at least one hours notice before urgent ICU admission (AUROC 0.91). The score has a sensitivity of 83% and specificity of 95% at a score of 8. In a multi-center validation study with 2074 patients the overall AUCROC was 0.87. We found the score performed well in sub-populations (Table 2). Amongst ‘case-patients’ the score increased over time

leading up to urgent ICU admission or code-blue event, and was independent of the number of risk factors for cardiac arrest (*Figure 3*). In clinical use we found the score was reliably calculated, with an Intraclass Correlation Co-efficient (ICC) of 0.92 (inter-rater reliability of score calculation).

[2] The Bedside-PEWS documentation record was developed using an iterative, multi-disciplinary approach and resulted in a documentation record with an embedded score calculation mechanism. In pre-clinical evaluation following their orientation to the documentation record, 96% of 98 frontline staff said the speed of use of the Bedside-PEWS Documentation Record was acceptable, and 97% said that the documentation record reinforced or improved their confidence in their clinical impression of the patient.

[3] Score-Matched care recommendations were developed using the responses of 280 healthcare professionals (*80 community, 200 referral*) surveyed to determine 'reasonable' care. For each survey, cluster analysis was used to identify similar recommendations, and from these score-matched care recommendations were developed for community and referral paediatric hospitals.

[4] The Education Program was developed by two nurse educators to support implementation and maintain expertise. It is based on over 35 years of nursing education experience and established educational principles. It includes the Bedside PEWS Instructor course and the frontline education program (*Figure 4, Appendix Bedside PEWS Instructor Course*).

Differences between Bedside PEWS and other approaches/systems

Differences include: [1] Complete integration of scoring into routine documentation. [2] Explicit institution-relevant, customizable care recommendations. [3] A scientifically developed and validated severity of illness score that is better at identifying patients at risk than the retrospective opinion of frontline nurses. [4] A nurse-educator developed, provider tested implementation program and [5] a pilot evaluation showing improved outcomes without additional resources (*Figure 5*).

1.2 What is/are the principal research question(s) to be addressed?

[1] What is the effect of the Bedside Paediatric Early Warning System on mortality and late detection of critical illness in hospitalized children?

[2] What is the effect of the Bedside Paediatric Early Warning System on processes of care for children admitted to inpatient wards?

[3] What is the effect of the Bedside Paediatric Early Warning System on resource utilization in children who are urgently admitted to the PICU?

Objectives

To evaluate the impact of the Bedside-PEWS on early identification of children at risk for near and actual cardiopulmonary arrest, hospital mortality, processes of care and ICU resource utilization.

Hypothesis

The Bedside-PEWS improves early detection of critical illness, reduces mortality and improves processes of care and does not increase healthcare resource utilization.

1.3 Why is a trial needed now?

[1] Sufficient preparatory work has been performed to establish that the Bedside-PEWS [a] can be safely implemented into clinical care, [b] performs better than alternative methods of identifying hospitalized children at risk of adverse outcome – including retrospective nurse opinion, [c] in pre-clinical and clinical use is acceptable to frontline providers, and [d] can be reliably calculated.

[2] Clinical practice 'norms' for early identification systems are not established - providing a 'timely' window of opportunity to conduct this trial. However there is increasing administrative and clinical interest in MET-RRT,⁷ in the context of a growing recognition that appropriate identification criteria are a pre-requisite to effective MET-RRT, or direct ICU consultation in hospitals without MET-RRT.^{6, 85}

[3] Currently in the US and Canada the majority of hospitals rely upon the 'expert' model to detect children at risk, and either do not have other explicit systems established, or (as in Ontario) are using unproven calling criteria, or are wondering (in the absence of data) which system to apply. Clinicians and administrators wish

to be involved in this trial, and will implement the Bedside PEWS in their hospitals if accordingly randomized. In the future pressure for 'action' may limit the feasibility of this trial.

[4] The problem persists. Near and actual cardiopulmonary arrest is frequent (~5000 times per year in US and Canadian hospitals), judged to be preventable, and current approaches have not had consistent or convincing effects on overall outcomes.^{1, 2, 7, 17, 51, 71, 82, 85} The consequences for individual children and their families are great, and the associated societal burden is significant.^{3, 4, 23} [5] In-hospital cardiopulmonary arrest is a sentinel event. Prevention is a patient safety imperative.

1.4 Systematic Reviews

A Cochrane review of adult outreach and early warning systems identified two randomized trials (Priestley 2004, Hillman 2005- see section 1.2).⁹⁵ A systematic review of paediatric MET-RRT and identification criteria was published by Winberg et al. in 2008.⁹⁶ The search identified 6 identification methods (all in our review) and 4 (pre-2008) studies of MET-RRT.^{17, 83, 84, 87}

A systematic review of adult and paediatric MET-RRT was published in 2010.⁹⁷ It identified five paediatric studies.^{17, 83-85, 87} The accompanying editorial questioned the benefits of MET-RRT.⁹⁸ Another review of adult early warning scores found good performance of adult scores in discriminating ICU from high dependency patients (AUCROC 0.83-86).⁹⁹ Others found scores and criteria predicting mortality poorly in adults.^{100, 101}

As part of the development of our original PEWS score we performed a systematic review of identification methods and individual vital signs. This unpublished data was used to guide item selection in the development of our original PEWS score.¹⁵ With an academic librarian we modified and re-ran this search: it identified 1,069 references (Table 3). After review, one additional study was identified. It was a single-center implementation of the Brighton score.¹⁰² Re-running this search in the Cochrane Library revealed no additional systematic reviews. There are no randomized trials of paediatric MET-RRT or of methods to identify children at risk of cardiopulmonary arrest.

1.5 How will the results of this trial be used?

The results of this trial will provide a scientific basis for local, regional, provincial and national decision-making, and for the recommendations of national and international bodies (International Liaison Committee on Resuscitation,¹⁰³ AHA, European Resuscitation Council¹⁰⁴) about cardiac arrest prevention and institutional best practices. Members of the study team are representatives in these committees, in hospitals, government and other organizations. If the trial is negative the costs of hospital-wide implementation can be avoided, resources more appropriately allocated, and the collaborative multi-site data set from the study used to develop and evaluate new hypotheses about cardiac arrest prevention and processes of care. If we find that Bedside-PEWS improves identification of children with evolving critical illness, and saves lives, then we have provided a scientific justification for the major system-level changes required for implementation and supported the creation of evidence-based policy.

1.6 Describe any risks to the safety of participants involved in the trial.

In control hospitals care will continue with established institutional practices (no additional risk). In hospitals randomized to implement, there are no known safety issues. Our pilot study suggests improved outcomes, and demonstrates that the Bedside PEWS can be safely used as part of the care of patients. The lack of proven efficacy of the Bedside PEWS (and other identification systems) creates the equipoise, supporting the need for the trial, and supporting the assertion that it is ethical to not implement the Bedside PEWS, other scores, or MET-RRT during the study.

2. THE PROPOSED TRIAL

2.1 Trial design

A cluster-randomized trial of the implementation of the Bedside Paediatric Early Warning System in hospitals with a paediatric intensive care unit (PICU) will be performed.

2.2 Trial interventions

[1] The Intervention: Bedside PEWS.

The Bedside PEWS is a documentation-based system of care that will replace existing documentation systems for vital signs in inpatient ward areas in hospitals randomized to receive the Bedside-PEWS. Frontline staff education within each hospital will occur over a period of three months preceding a 5 week run-in implementation phase, which will be followed by hospital-wide implementation. The Bedside-PEWS documentation record will become the primary method of documentation for vital signs and related data. The Bedside-PEWS score matched care recommendations will have the titles of nursing, physician and ICU teams modified to match the local vernacular. These site-relevant score matched care recommendations will be included in each documentation record, on clipboards and pocket-cards in English and French versions of Bedside-PEWS.

Hospitals with electronic health records that include the 7 items of the Bedside PEWS will be modified so that the Bedside PEWS documentation record is embedded into the clinical data entry step. This has been achieved at one center, and we are creating a standard template to assist implementation in other sites with existing electronic medical record systems.

Preparing for Implementation

Implementation will be conducted in 7 phases (Table 4).

[1] Meeting Local Documentation Standards. The Bedside PEWS documentation record will be customized to meet the documentation standards of each hospital.

[2] Matching the local vernacular. The language used in the score-matched care recommendations will be modified to match local norms. Draft copies of the documentation record will be printed and circulated for local approval before printing.

[3] Bedside PEWS Instructor Course. Nurse educators and the physician lead will attend the 2-day Bedside PEWS Instructor course. The meeting will occur 2-4 months before clinical implementation begins. This conference is comprised of an introduction to the Bedside PEWS (rationale, development, scientific basis, components of Bedside PEWS, Bedside PEWS materials, frontline staff education sessions, frequently asked questions, and in-session evaluations). The expected outcomes of the Bedside PEWS Instructor course and meeting are (a) demonstration of technical competence, (b) description of the implementation environment, (c) articulation of an implementation plan, (d) making a plan for ongoing communication with the Bedside PEWS educators, and [4] below.

[4] Articulating the site-specific plan for run-in and hospital-wide implementation.

[5] Frontline staff education. Nurse educators and the physician lead will conduct frontline staff education sessions to educate the frontline paediatric staff at their center. Training will occur over the 4-month period, beginning 3 months before the start of the run-in implementation. Training will include 2-hour small-group (6-8 person per educator) education sessions, and 1-2 hours of interactive use of the Bedside PEWS documentation record as we have done previously. Our evaluation of 98 frontline staff showed that this education program is effective and appropriate and could be conducted easily over 5-6 weeks (*Figure 4*).

The technical competence of frontline staff with Bedside PEWS after training will be assessed following the frontline staff education sessions as follows: each will document a total of 10 sets of vital signs from 3 relevant case scenarios selected by the Bedside PEWS Instructor from the on-line Bedside PEWS case library (to be created from our paper-based library of 120 scenarios). All participants will chart on paper documentation records – irrespective of the documentation system in their institution. The calculated score will be compared with the ‘gold’ standard score that is electronically calculated. Individuals will be regarded as ‘competent’ if their intraclass correlation co-efficient (ICC) is >0.90 , and they have no scores more than 2

different than the electronically calculated score. Staff identified as having difficulty with scoring will be provided additional training and re-evaluated. Our experience, training 120 staff, identified no staff that required additional training. We found the ICC for scoring of the Bedside PEWS score comparing Bedside PEWS educators with newly trained staff was 0.92 and in real patients there was an ICC of 0.90 for repeated scoring of 786 scores. One score was more than 2 points different between the frontline RN and the Bedside PEWS RN (*accepted JPCH*).

[6] A run-in phase will permit phased implementation in each hospital. This will permit focussed implementation in pre-specified hospital wards, identification of local challenges and implementation of effective solutions. The solutions will be drawn from local knowledge, from the Bedside PEWS team, and from the experiences of other implementing sites. Information sharing will be facilitated by teleconferences. For 4 days per week, beginning the first day of the second week of implementation, study staff will review the most recent 12 hours of documentation from 10-15 randomly selected patients for whom the Bedside PEWS documentation record is being used. At the end of each week a minimum of 40 12-hour periods of documentation will have been assessed. Rates of accurate score calculation, (Aim: >80% of calculated scores within 2 points), score completeness (Aim: ≥ 5 of 7 score items used for >80% of scores calculated), and the frequency of vital sign assessment (Aim: >80% of patients within recommendations) will be determined for patients assessed each week.

These data will be used to guide the Bedside PEWS instructors, other local educators, and frontline staff. Interim data will be reviewed at least twice per week. The data from hospitals not achieving targets by the fourth week will be reviewed by the study executive steering committee to evaluate the appropriateness of implementation at that site.

[7] Hospital-wide Implementation will occur on the specified date. (5 weeks after the completion of the 26 week baseline period). Following implementation local nurse educators and the physician lead will provide ongoing frontline staff support, complemented by regular teleconferences and site visits.

Control Hospitals: Standard Care. Hospitals randomized to standard care will continue with established methods of care. This will include the use of calling criteria and/or the expert model to identify children at risk. As in intervention hospitals, existing MET-RRT practices, established staffing and documentation practices will continue.

2.3 Allocation of participating hospitals to trial groups

Randomization will be balanced within two strata; hospital size (<200 vs. ≥ 200 eligible inpatient ward beds). Within each stratum half the hospitals will be randomly selected to receive Bedside PEWS, while the remaining hospitals will comprise the control arm. Allocation will be concealed until the start of the study measurements and will be revealed in the 2nd week after the start of data collection at each site (*Figure 6*). The 6-month baseline period will be used to prepare for implementation in hospitals randomized to the Bedside PEWS intervention.

2.4 Proposed methods for protecting against sources of bias

As in previous randomized^{82, 88} and before-after studies⁸³⁻⁸⁷ of MET-RRT, the nature of the study will not permit blinding of allocation to personnel in participating hospitals nor of the site co-ordinators assessing outcomes. In addition to randomization, the study design employs the following approaches to reduce bias:

- [1] Balanced randomization of hospitals (as described above).

- [2] Minimization of contamination. This will be achieved by [a] randomization at the hospital level, as recommended by Tibballs,⁸⁶ [b] separation of personnel from hospitals randomized to each arm of the study. This will be achieved by having separate training and study meetings for study personnel randomized to alternate arms of the trial. [c] In addition, the project manager and the Bedside PEWS research assistants will be instructed not to discuss the details of the Bedside PEWS intervention with staff from hospitals randomized to standard care.

- [3] Using objective reproducible outcomes measured using standardized approaches and quality control. This will be achieved by site co-ordinator training, and site inspections from the Project Manager/Bedside PEWS study co-ordinators and the PI.

[4] Using blinded adjudication of the potential preventability of cardiac arrests.

[5] By blinding the analytic team to allocation.

[6] Evaluating baseline event rates will improve the interpretation the trial results. The presence of a 'Hawthorne' or contamination effect from being studied will be evaluated and adjusted by use of baseline measurements of clinical and process of care outcomes. In the MERIT cluster RCT study of adult MET-RRT event rates reduced from baseline to intervention period in both intervention and control hospitals.⁸²

2.5 Inclusion/exclusion criteria

Inclusion: Participating hospitals will constitute the clusters randomized in this trial. Eligible hospitals will provide care for more than 200 inpatient admissions aged <18 years and >37 weeks gestational age in eligible inpatient wards each year. Eligible hospitals will have specialised paediatric physicians (including paediatricians, paediatric surgeons, other paediatric sub-specialists) and, one or more intensive care unit (PICU) that provides care for children. A PICU is a designated, staffed area for prolonged mechanical ventilation, invasive monitoring and circulatory support for children- including but not limited to neonates. Other areas designated for patients of increased acuity, such as 'constant observation' or 'high dependency' or 'step-down' units will be regarded as part of the PICU where the PICU staff physicians are wholly or jointly responsible for the care of children in these areas (can write orders in the chart).

Participating hospitals may or may not have a MET-RRT for children. A MET-RRT is defined as an identified team of one or more trained healthcare professionals who report to an on service PICU physician, and perform urgent consultations on hospital inpatients.⁷⁴

Eligible inpatient wards are areas where care is provided to patients who are admitted to the hospital, other than PICU, operating rooms, and other designated areas where anaesthetist-supervised procedures are performed. Admitted patients cared for in emergency departments will be regarded as in an eligible 'ward' if the documentation format is the same in the emergency department as in the inpatient ward. If the emergency department continues to use a separate 'emergency department' documentation record for admitted patients then the emergency department will be deemed an ineligible area. This distinction is based on the potential for changed documentation if the hospital is randomized to implement the Bedside PEWS. All eligible inpatient wards will participate in the study. **Eligible patients:** Within eligible hospitals we will study patients older than 37 weeks gestational age and less than 18 years who are admitted to eligible inpatient wards, who receive care in an eligible inpatient area during the study.

Exclusions: We will exclude hospitals that have plans to introduce a new 'medical emergency team' during the study, and where a severity of illness score (Brighton, Cardiff, PEWS, Bedside PEWS or other unpublished score) is used in ward areas, and in hospitals where randomization is not deemed acceptable. These exclusion criteria ensure that major system changes including introduction of MET-RRT, new documentation systems, physician staffing, and hospital capacity will not bias results.

Excluded patients will be those who are less than 37 weeks gestational age throughout their hospitalization, patients who are cared for exclusively in an NICU, and children who are admitted directly to a PICU and die before PICU discharge and thus have not received care in an eligible inpatient ward. These children have not been exposed to the intervention / control 'treatment' as they have not been in an eligible inpatient ward.

2.6 Duration of treatment

The intervention period will be for 12 months (52 weeks). This will begin 7 months (31 weeks) from the start of baseline data collection at that hospital. A 1-year period has been chosen for 3 reasons: [1] to reduce the effects of seasonal variation. Studies of less than 12 months may be affected by systematic differences in patient volume and outcomes related to seasonal illness. [2] A multi-year intervention period (ie 2 years or longer) requires a significantly greater period of observation and greater commitment from each hospital, limiting study feasibility. [3] Timely completion of the study is concordant with decision-making needs, and is feasible with the available number of sites.

2.7 Follow up frequency and duration

Outcomes will be prospectively assessed for 6 months (26 weeks) to provide baseline data. Then following the 5-week period (during which the run in will occur in intervention hospitals) outcomes will be

prospectively assessed for 12 months (52 weeks, *Figure 6*). The timing and duration of outcome assessment will be the same in intervention and control hospitals, and will total 18 months (6 month baseline and 12 months 'intervention period' for a total of 78 weeks) irrespective of treatment allocation.

2.8 Outcome measures

Primary Outcome: All Cause Hospital Mortality.

All cause hospital mortality will include all deaths of eligible inpatients who were cared for in an eligible inpatient ward during their hospital stay. This includes anticipated deaths in children with 'Do Not Resuscitate' orders. Deaths in children cared for exclusively in the PICU, NICU, Emergency Department (or combinations of these) will be excluded as these children have not been cared for in an inpatient ward eligible for implementation of the Bedside PEWS.

Rationale: [1] The objectivity and reliability of measurement makes all cause hospital mortality an ideal primary outcome in this trial. [2] Reduced all cause hospital mortality is the goal of any intervention to improve the outcomes of care, and as such should be a major focus of evaluations to improve the outcomes of hospitalized children. [3] Other studies of MET-RRT (using before and after design over many years) have reported reduced all cause mortality^{84, 86} underscoring the clinical relevance of all cause mortality. [4] Most deaths in children receiving cardiopulmonary resuscitation occur during the index hospitalization. In our 6-year study of in-ICU cardiac arrest we found one (1.4%) additional death after hospital discharge and within 12 month of the index cardiac arrest. This is consistent with other studies showing that most hospitalized children who die, die in hospital.^{105, 106, 107, 108} [5] The effect of palliative care services on place of death is small.^{107, 109-112} One large US study found the proportion of deaths in hospital reduced by less than 6% (from 85.7 to 80.1%) over a 10 year period.¹¹⁰ [6] All cause mortality is an established quality metric in Canadian and British adult hospitals, and is publicly reported as the Standardized Mortality Ratio in Ontario Hospitals.^{46, 47, 113-115} [7] While death with 'DNR' vs. 'unexpected' deaths (no DNR), has been used as a definition to separate 'preventable' from 'unpreventable' deaths following acute events in adult patients (in-hospital cardiac arrest),^{82, 116} in hospitalized children there are significant limitations to the use of the DNR orders to make this distinction. First, DNR orders reflect *current expectations* of outcome and do not reflect the 'preventability' of the preceding clinical events. Second, the majority of deaths in hospitalized children occur remote from the clinical deterioration event (days),^{2, 4, 19, 54, 57, 117} in contrast to relatively short time (hours) between DNR order and death.¹¹⁸⁻¹²⁰ This suggests that the outcome of the earlier (and potentially modifiable) resuscitation event is influencing the DNR discussions and decision-making, providing further support to the notion that DNR and preventable deaths are separate concepts. Conversely, 'futile' resuscitation may be performed on hospitalized children.¹²¹ We will evaluate the frequency of DNR orders and perform analyses of patients with and without DNR. [8] The lead author of the Harvard Medical Practice Study asserted that all cause hospital mortality is a better measure of quality of care than 'preventable' death.¹²² [9] Other, objective and reproducible assessments of 'preventable' are challenging and resource intense.¹²³⁻¹²⁶ Notwithstanding these limitations, we will evaluate the potential preventability of cardiac arrest as described below.

Secondary Outcomes

The main secondary outcome is the **Significant Clinical Deterioration Event**. This is a composite outcome comprised of the treatment(s) provided or death prior to transfer from an inpatient ward (Table 5). A significant clinical deterioration event will be defined as the provision of significant respiratory or circulatory therapies or cardiopulmonary resuscitation in the 12 hours before transfer from inpatient ward or the one hour after transfer, or death without DNR order in an inpatient ward. Transfer is defined as a patient transfer from an inpatient ward to a PICU. This outcome excludes patients with DNR orders – and is thus a measure of the timeliness of interventions in children for whom active resuscitation is anticipated.

Rationale: [1] Experience and our data suggest that Significant Clinical Deterioration Events are associated with increased risk of mortality and acquired neuro-cognitive morbidity, and reduced quality of life.⁵ [2] Significant clinical deterioration represents one of the 'worst' safety outcomes following care in hospitals. If significant clinical deterioration events can be reduced or prevented by the Bedside-PEWS this will be a major advance in patient safety. [3] Composite outcomes composed of relevant components – including

death are frequently used in clinical trials including the MERIT study of adult MET-RRT⁶² and in other CIHR funded paediatric critical care trials.^{48, 49} [4] Rather than reporting the frontline staff perception of need – as indicated by the code blue call, the significant clinical deterioration event is a measure of the treatment provided to each patient. [5] Our single center before–after evaluation showed fewer Significant Clinical Deterioration Events with Bedside-PEWS (*Accepted JPCH 2010*). [6] This measure has been presented to, and approved by, the members of the Canadian Critical Care Trials Group (CCCTG) and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI).

Secondary outcomes: Clinical

Eight additional clinical outcomes will be recorded.

[1] The nature of clinical deterioration events. This outcome is rated on the seven-point Children's Resuscitation Intensity Scale (Table 5). This scale is comprised of the treatment(s) provided in the 12 hours before transfer to PICU, and death prior to transfer in patients admitted either [a] directly from an inpatient ward or [b] from an inpatient ward via the operating theatre –when the urgent PICU admission was initiated in the eligible inpatient ward. Urgent PICU admissions that are initiated when the patient is in the operating room will not be regarded as clinical deterioration events.

Treatments include non-invasive and invasive respiratory support, circulatory support (intravascular fluids, inotropes and mechanical support) and combinations of these. The scale includes interventions performed in the first hour after ICU admission (intubation, cardiopulmonary resuscitation, starting mechanical circulatory support).

The nature of clinical deterioration events is a measure of the timeliness of interventions in children for whom active resuscitation is anticipated. Thus we exclude patients with 'Do Not Resuscitate' (DNR) orders or equivalent if these are in place *before* cardiac or respiratory arrest. This approach ensures [1] the *inclusion* of patients where cardiopulmonary resuscitation was started, was subsequently deemed futile, and then was stopped using a DNR-type order, and [2] the exclusion of patients who have an anticipated death with DNR order in place.

[2] Potentially preventable cardiac arrest will be evaluated in all patients who had a cardiac arrest while in an eligible inpatient ward, without a preceding DNR order (rated as 6 or 7 on the Children's Resuscitation Intensity Scale). In this study potential preventability is defined as the degree to which 'events may have been avoided given the application of reasonable current (2011) standards of practice by an average practitioner and system anticipated to manage the condition in question'. This subjective definition is based on those used previously in adverse event studies.^{9, 11, 14, 126, 127}

Potential preventability of cardiac arrest events will be rated on the 6-point scale used in the Quality in Australian Health Care Study and the Canadian Adverse Event Study (Table 7).^{9, 126} Events with a consensus rating of at ≥ 4 will be regarded as potentially preventable cardiac arrests. Thus potential preventability ratings of 4: 'more than likely (more than 50/50, but "close call")', 5: 'Strong evidence of preventability', and 6: 'Virtually certain evidence of preventability' will be deemed potentially preventable cardiac arrest events.

The potentially preventability of cardiac arrest events will be determined using the opinion of blinded reviewers. Reviewers will be selected as follows: Candidate reviewers (physicians with >5 years independent practice in a paediatric hospital) will receive standardized instruction about the definitions (above), the scoring method, will participate in a group meeting to discuss potential examples of events for review, and will each complete 20 reviews of practice cases from the Bedside PEWS library. The Executive Steering Committee will review the anonymized results of these initial ratings, and make the final determination of which reviewers will perform the rate the potential preventability. An intraclass correlation co-efficient will be calculated to represent the inter-rater reliability of the selected reviewers.

Following this preparation the event reviews will be conducted to determine the consensus rating. Two expert physician reviewers will independently review clinical data from each event. Clinical data from each significant clinical deterioration event where a cardiac arrest occurred will be abstracted (Table 6, Case Report Form) and presented in a standardized format for review. The patient data will be anonymized and delinked, and hospital identifiers will be anonymized before adjudication panel review.

The goal of the independent rating by the two reviewers is to obtain a consensus rating. For events where potential preventability ratings are concordant, this rating will be used as the consensus rating. For discordant ratings the reviewers will discuss the event and agree on a consensus rating. If a consensus cannot be reached between the initial reviewers after discussion then a third reviewer (who has >10 years paediatric hospital practice) will become involved. The third reviewer will review the data of the event, and discuss with the two reviewers to facilitate consensus. The resulting rating will be used as the consensus rating. If consensus between the two initial reviewers still cannot be reached then the opinion of the third reviewer will be used as the consensus rating. We will report the kappa for the independent ratings (before discussion) of the two reviewers. Potentially preventable cardiac arrest events will be expressed per thousand patient days. Additional methodologic evaluations of approaches to the assessment of potential preventability will use this dataset (with delinked patient identifiers and hospital data).

[3] Unplanned re-admission to hospital within 48 hours of hospital discharge. This outcome will be operationalized as re-admission before midnight of the second day of discharge. Thus re-admission will occur before the 3rd midnight following hospital discharge.

For all eligible patients discharged from a PICU to an eligible hospital ward we will record:

[4] Unplanned PICU readmission within 48 hours of PICU discharge. Again this will be operationalized as readmission to PICU before midnight of the second complete day following PICU discharge (or stated alternately; before the third midnight following PICU discharge).

PICU mortality, and unplanned re-admission (hospital, PICU) will be represented per thousand hospital discharges.

In patients urgently admitted to the PICU from a hospital inpatient ward we will measure:

[5] PIM score predicted risk of mortality.^{43, 128}

[6] PICU mortality.

[7] The PELOD score for PICU stay and the first 24 hours in PICU.¹²⁹

[8] Ventilator free days (days alive and without invasive mechanical ventilation) in the 28 days beginning at PICU admission will be recorded for the first PICU admission during each of the baseline and the post-randomization periods. Patients with repeat PICU admissions will have all other in-ICU outcomes recorded. Exclusion of measurement of ventilator free days from PICU re-admissions will avoid double counting resulting in the attribution of ventilated days from the second urgent PICU admission to the first PICU admission.

Urgent PICU admission is an admission to PICU with departure from the event location in <6 hours from the time the PICU admission was initiated. Initiation is the time that the PICU admission is confirmed, or confirmed as a 'definite possibility following surgery' in cases where post-operative care in the PICU might (might not) be required. PICU admissions initiated in the OR are also regarded as urgent ICU admissions, irrespective of the time between initiation and departure from the OR.

Secondary outcomes: Process of care

The study includes 5 process of care assessments.

[1] 'Stat' calls will be defined as those requesting immediate physician attendance to provide patient care to a patient admitted to an inpatient ward.

[2] Code Blue calls for immediate medical assistance of the resuscitation team and equipment.

[3] Urgent consultations to the ICU or MET-RRT will be recorded. The total number of new consultation episodes will be counted. Patients who have been previously consulted on will be regarded as having a new consult if an urgent call is made that results in an unplanned or earlier than planned review. We will exclude planned review visits by the ICU team or the MET-RRT.

[4] Documentation. The frequency that each of the 'vital' signs (HR, RR, SBP, Temperature) and the other 4 signs of the Bedside PEWS score (Transcutaneous oxygen saturation, respiratory effort, oxygen therapy, capillary refill) are documented in 24 hours will be recorded from five randomly (*central computerized randomization*) selected patients each week. We will review documented physician visits, the nurse patient ratio

and the use of continuous monitoring. [5] Frontline staff will complete the documentation and interaction survey (2 pages, <10 minutes to complete) that describes their perceptions of the documentation system, and the nature of interactions with physicians (*Appendix Questionnaire*).

Secondary outcomes: Resource Utilization

Resource utilization will be assessed in all hospitals by measuring Hospital Length of Stay, and following urgent ICU admission, ICU Length of Stay and the use of ICU technologies: mechanical ventilation (ventilator days), haemodialysis (dialysis days), ECMO (days) and Days with Nitric Oxide while in the ICU. 'Dialysis' will include haemo-filtration and haemodialysis techniques used either intermittently and continuously (or both), peritoneal dialysis, plasmapheresis, and red-cell exchange.

Exit Survey

Three months after the end of the 12 month intervention period we will conduct a survey of site-investigators and administrative leads. The survey will ask about the planned actions of each site with respect to the use of Bedside PEWS. This will provide important information about intended use outside the research context. We will compare the before –after event rates of hospitals that implemented Bedside PEWS with the plans made by local decision-makers. Eligible decision-makers will include; Hospital Chief Executive Officers (CEOs), Chief Nursing Officers (CNO), Vice Presidents, and heads of a clinical departments, divisions or services. Eligible services include senior nursing administrators for inpatient ward areas, resuscitation committee heads, and medical emergency team leaders.

At each hospital a maximum of 10 eligible leaders will be selected by the EPOCH study team. A minimum of 4 decision-makers will be identified the CEO, the CNO, the clinical head of paediatric surgery and the clinical head of paediatric medicine. Hospitals with more than 80 beds will identify 2 additional decision-makers; hospitals with more than 120 beds will identify 4 additional decision-makers, and hospitals with more than 180 beds will identify an additional 6 decision-makers. The identified decision-makers will be approached by a neutral third-party peer to introduce the study. Decision-makers indicating interest in the study will then be contacted by the site investigator or their delegate to discuss completion of the survey.

2.9 Study measurements

Study measurements will be prospectively recorded by trained site co-ordinators, and will be distilled from multiple overlapping sources: [1] real-time reports from hospital information systems; [2] written admission/discharge records in PICU and other areas; [3] hospital switchboard paging logs; [4] mortuary logs; [5] code-blue team logs, [6] from clerical and clinical staff; and [7] from the medical records as we have done successfully in our prior studies.

In all hospitals, site co-ordinators will record the numbers of hospital discharges, inpatient ward-days, and ICU discharges and ICU-days at hospital discharge. Patient days will be defined as the presence of a patient in the designated area for all or part of a 24-hour day (00:00–23:59). Hospital days will include all eligible-patient days where patients are admitted to hospital inpatient wards (not PICU, NICU), and ICU days will be defined as whole or part days in PICU. At the end of baseline and intervention periods patients will be regarded as discharged from the hospital (inpatient ward and PICU).

Hospital characteristics will be recorded at 4 time periods after the start of study measurements [1] in the first week, [2] in the 5th month (in week 22, 23 or 24), [3] in the 12th month (in week 54, 55 or 56) and [4] in the last month of the intervention period (in week 81, 82 or 83). This will enable evaluation of organizational stability within participating hospitals.

All-cause hospital mortality and ICU mortality will be measured by reviewing the medical records of all children dying in hospital. Screening will include review of mortuary logs and PICU discharge documentation. The presence and date-time of DNR order at the time of death will be recorded. Code-blue calls to resuscitation teams, stat calls for physicians, and unplanned hospital readmission will be prospectively screened. Each event will be identified and confirmed as for an eligible patient who was cared for in an eligible inpatient ward. Clinical deterioration events will be measured by daily review of intra-facility transfers to PICU and of deaths in inpatient wards. The nature of each clinical deterioration event will be determined by medical record review (Table 5). The medical record of identified patients will be reviewed to determine

that the child had been cared for in an eligible area (inpatient ward), if there was a documented DNR order at the time of death (and before cardiopulmonary resuscitation if this was provided) and the place of death (PICU or other).

Potentially preventable cardiac arrest events will have demographic information and current clinical data, including 13 hours vital signs, current investigations and interventions will be abstracted (Table 6), verified by the site investigator, patient identifiers removed and submitted for blinded rating of potential preventability.

Documentation frequency. Five randomly selected patients will be identified each week. Local study evaluators will document the number of times each 'vital' sign (HR, RR, SBP, temperature) and other signs within the Bedside PEWS score (transcutaneous oxygen saturation, respiratory effort, oxygen therapy, capillary refill) were documented in the preceding 24 hours (*Appendix: Case Report Form*). The documentation and interaction survey (*Appendix: Questionnaire*) will be administered to all frontline staff by the site co-ordinator, 2 months into the baseline and 3 and 9 months after the start of the randomization phase.

ICU outcomes and resource utilization in patients who are admitted urgently to an ICU will be measured as follows: Site co-ordinators will prospectively record ICU days, PELOD score for the duration of ICU stay, days of ICU resource utilization, ventilator free days and ICU survival. Data will be reviewed at the time of site visits, and 5% of randomly selected records will be compared with source data by the Bedside-PEWS Study coordinator.

In hospitals randomized to implement Bedside PEWS, implementation data will be reported (*anonymized*) from implementing hospitals in real time, by a secure web-based linkage (*Appendix: Research IT*). This approach will permit rapid creation of reports indicating agreement between trainee and trainer, concordance with computer-calculated scores, completeness of scoring, and adherence to recommendations.

We have significant previous experience with primary collection and co-ordinating multi-site data (*Bedside PEWS, Ontario PCCRT collaborative, other previous multi-center trials*). Each site co-ordinator will update a local clinical database and report de-identified data to the study co-ordinating center *via* secure web connection (256 bit encryption). Completed anonymous surveys and the review of documentation practice will be copied and sent by registered mail and/or sent by facsimile to the study co-ordinating center for data entry.

2.10 Health service research issues

This trial directly and indirectly addresses health-service and health-economic issues: [1] The study will provide a scientific basis for decision-making about a hospital-level intervention. This intervention requires allocation of healthcare resources for its implementation and maintenance. [2] While quality of life is not measured due to limitations of resources, our preliminary work shows that children receiving more resuscitation have lower quality of life and greater neurocognitive deficits.⁵ [3] The current study will evaluate differences in the use of resource intense ICU therapies (ventilation, dialysis, plasmapheresis, ECMO, and nitric oxide days) in hospitals with and without Bedside PEWS.

2.11 Sample size and assumptions

Power calculations were based on population estimates derived from local data using a published method for cluster RCTs.¹³⁰ For all cause mortality in referral hospitals we found a baseline rate of 5.1 per thousand (data from 14 hospitals). The steering committee agreed that a mortality reduction of less than 1/1000 admissions would not be a compelling reason to modify practice. A study with 20 hospitals can show an 18% relative risk reduction in mortality (Absolute Risk Reduction 0.09%), given $\alpha=0.05$ (2-sided), power=80%, mean of 119 paediatric beds, length of stay=4 days, with 0.90 average occupancy, $k=0.15$, $n=20$, baseline rate= 5.1/1000. The quantity k is the coefficient of variation for mortality between hospitals. Allowing for the potential attrition of 1-2 hospitals during the study we will study 22 hospitals.

Available data from participating hospitals indicates that randomization will occur in sites with a total of 2322 beds; 99,389 patient admissions, admitted for 397,556 patient days (hospital length of stay 4 days). Data from 4 paediatric hospitals in Ontario describes 1052 Urgent ICU admissions/ year, of which we estimate (Figure 1) 40% are Significant Clinical Deterioration Events (SCDE), for a rate of 2 per thousand patient days. Thus with 20 sites we will be able to show a 31% reduction in SCDE ($\alpha = 0.05$ (2-sided) power =

80%, $k = 0.15$, where k is the coefficient of variation for SCDE rate between hospitals). The assumption of a modest k is consistent with an analytic approach using baseline rates (Sample Size Appendix).

2.12 Participation

We will recruit the first 22 hospitals (~2300 inpatient beds) with REB approval. The Bedside-PEWS is a hospital-level intervention modifying documentation in hospital inpatient wards. As such all (~100,000) eligible inpatients will be 'involved' in the trial.

The investigators believe that patient-level consent should not be required for five main reasons: First, the local documentation system is 'inherited' by patients as a part of routine hospital practice. This approach to documentation is applied to all patients. Hospitals implementing Bedside PEWS have elected to adopt this as the standard approach in their hospital. Control hospitals continue established practices. Consent for routine documentation practice (and other practices including staffing, ICU consultation, physician review) is implied with hospital admission. Consequently, a requirement for consent to receive the routine practice seems counter-intuitive. Second, the patient-level data is retrospectively obtained, does not require additional clinical investigation, and there is no contact with patients or their families. We have conducted similar data reviews in paediatric hospitals in Canada and the United Kingdom without patient consent. Third, obtaining consent to describe clinical deterioration events that have not occurred (and that may not occur) is potentially distressing to families and is inefficient use of research resources. Fourth, consent for the participation of 100,000 patients is not feasible, and if required would significantly undermine the scientific validity of the study. Finally, data will be presented in aggregate. No identifying information will leave the study office in the participating hospital. Furthermore, in our assessment of potentially preventable cardiac arrests we will delink the evaluated data from patient-level identifiers.

Individual-level consent from healthcare professionals will be obtained as deemed appropriate for staff surveys and the post-study survey of administrative intent. In our previous use of the anonymously completed documentation and interaction survey, participant consent has been implied by survey completion. This approach has worked well for participants and the study teams involved.

2.13 Compliance

Implementation of the Bedside-PEWS is a major knowledge translation activity. It involves training, and subsequent collaboration with the Bedside-PEWS Instructors at implementing hospitals, effective delivery of the education program, uptake of education the frontline staff, and clinical application. Potential issues with compliance to study procedures will be managed as follows: [1] Centralized training (Bedside-PEWS Instructor course). [2] Explicit articulation of goals and timelines for each study site. [3] The intervention includes a 5-week run-in period of implementation in 20-30 beds. This run-in phase will permit hospitals randomized to implement the Bedside PEWS to have focussed local application, real-time evaluation of performance, and feedback to optimize implementation, and create a local template for successful implementation. [4] Review of documentation (implementing sites) will be used to assess the compliance with vital sign documentation and score calculation, using site-specific reports. [5] Formal Review of #2, #3 in weekly teleconferences. [6] Scheduled site visits by members of the study team, and [7] additional site visits as required.

2.14 Loss to follow up

We do not anticipate loss to follow up of hospitals or patients within hospitals. In the calculation of ventilator free days we will assume that patients who are discharged from hospital within 28 days of urgent ICU admission are alive and without a ventilator.

2.15 How many centers will be involved?

The study will involve 22 hospitals. The inclusion of international sites provides a greater variety and number of hospitals ensuring adequate power to identify clinically important differences and increasing the generalizability.

2.16 Analysis

Demographic and unadjusted outcomes data will be reported using means, median, variances, inter-quartile ranges, or as proportions with 95% confidence intervals. Outcomes will be reported for the baseline and intervention periods for each hospital consistent with published recommendations for cluster randomized trials.¹³¹ Baseline event rates will be determined using 6 months of prospective data.

Primary analysis: All-cause hospital mortality will be evaluated using a logit regression model. The dependent variable will be the logit of the proportion dying in each hospital. The independent variables will include a dummy indicator for treatment arm, the baseline mortality logit and the hospital size stratification variable. The analysis will be weighted by the size of the hospital.

Secondary Analyses: An identical logit model will be used for (a) ICU-mortality after urgent ICU admission where the PICU admission was initiated in a hospital ward, (b) ICU-mortality after urgent ICU admission initiated in the OR, (c) unplanned hospital re-admission within 48 hr of hospital discharge and (d) all cause mortality following DNR orders. Significant Clinical Deterioration Events, code blue events, stat calls and urgent ICU consultations per 1000 patient-days will be evaluated using Poisson regression using hospital-level aggregated count data. The independent variables will include a dummy indicator for treatment arm, the baseline event rate and the hospital size stratification variable. A linear regression model, in which the within-hospital mean is the dependent variable, will be used to evaluate (a) the nature of clinical deterioration events, (b) inpatient ward patient-days, and in patients urgently admitted to PICU: (c) the PIM2 score, (d) the PELOD score, (e) ventilator free days, (f) ICU-patient days, and (g) ICU therapy days (each of mechanical ventilation, ECMO, dialysis, plasmapheresis and nitric oxide use). The independent variables will include a dummy indicator for treatment arm, the baseline means and the hospital size stratification variable. The analysis will be weighted by the size of the hospital.

An identical linear regression model will be used to evaluate the frequency of vital sign documentation from the randomly selected patient records. Since the number of records abstracted will be the same in each hospital, weighting will not be necessary. Documentation will be evaluated as follows: the number of Heart Rate, Respiratory Rate, Systolic Blood Pressure, Trans-cutaneous oxygen saturation, Capillary Refill, oxygen therapy and respiratory effort measurements, and the number of times that all seven items were documented for the randomly selected patients, will be compared for patients in hospitals with and without Bedside PEWS. All analyses will adjust for baseline event rates and hospital strata. Linear regression will be used to compare the numbers of [1] vital signs documented, [2] documented physician visits, [3] the nurse patient ratio and the use of [4] continuous ECG monitoring and [5] continuous pulse oximeter monitoring will be made with the Bedside PEWS scores calculated from the abstracted clinical data.

Analysis of the documentation and interaction survey, the post Bedside PEWS education survey and the post-study decision-maker survey data will be descriptive. Comparisons will be made between groups using linear regression weighted by the size of the hospital.

A-priori Subgroup analyses

The following sub-group analyses will be performed. [1] Hospital size. Hospitals will be classified on the basis of the number of eligible inpatient ward beds. Hospitals with 200 or more eligible inpatient ward beds will constitute one group and those with less than 200 eligible inpatient ward beds the other. This consistent with the stratification method used for randomization. [2] Hospitals with and without medical emergency teams. [3] Hospitals with ECMO for children. [4] patients with urgent PICU admission initiated in an inpatient ward.

The study outcome analyses will be performed once. There will be no interim analysis. Dr A Willan (senior statistician and co-investigator) will supervise and assume responsibility for analyses. He will report the findings to the Executive Steering Committee for clinical interpretation.

In addition, exploratory analyses will evaluate the relationships between responses to the post Bedside PEWS education survey and in the results of [1] the documentation and interaction surveys and [2] the vital sign documentation review in these hospitals as part of a thesis project.

3. TRIAL MANAGEMENT

3.1 Day-to-day management of the trial

The project manager will be responsible for day-day trial management, and will report to Dr Parshuram (PI) and the Executive Steering Committee. At each hospital the site-investigator will work with the project manager to formalize inter-institutional agreements, obtain ethics board approval and appoint the local site-coordinator. In the first week of data collection the hospital randomization will occur. Web-based randomization will be supervised by the statistician co-Investigator Dr. Willan. Site investigators and local administrative leads will be notified of the result of randomization within 10 days of the start of data collection.

The study co-ordinating center will be in the Center for Safety Research at the Hospital for Sick Children, Toronto. The study staff (*Project Manager, Research Assistants, and Bedside PEWS Educators, analyst, web manager, statistician and students*) will be housed within the offices of the Center, and supported by infrastructure of the Child Health Evaluative Sciences Program of the Research Institute of the Hospital for Sick Children. The Bedside PEWS Instructor Program sessions will be conducted within the SickKids Learning Institute, and will use the tele-video-conference facilities of the Hospital.

3.2 Trial Administration

The trial administrative structure is comprised of the PI, the executive steering committee, site-investigator co-applicants, and collaborators. The PI (Parshuram) will assume overall responsibility for the conduct of the study, will supervise the central study team, and chair the executive steering committee. Dr Willan (statistician and Senior Scientist of the Research Institute at the Hospital for Sick Children) will be responsible for the analysis of the trial, and will create the report of the study results. Prior to the submission of this report to the Executive Steering Committee, an independent statistician will review the primary data, analyses and the report. The independent statistician will provide supplementary annotations as required. Upon receipt of the report, the Executive Steering Committee will interpret the results and form a writing committee for manuscript creation.

The Executive Steering Committee is comprised of Dr. Christopher S Parshuram who is also the executive steering committee chair. The committee members are Dr. Ari Joffe, Dr. Andy Willan, Dr. Betsy Hunt, Dr. Catherine Farrell, Dr. David Wensley, Dr. Jamie Hutchison, Dr. Jacques LaCroix, Ms. Karen Dryden-Palmer, Dr. Martin Gray, Dr. Mark Helfaer, Dr. Patricia Parkin, Dr. Ron Gottesman and Dr. Vinay Nadkarni.

The Site-Investigators will be directly responsible for conduct of the study at their hospital, including working with the Project Manager to obtain research ethics approval, and to appoint, then support and supervise the Site Coordinator throughout the study. Site investigators will be responsible for the integrity of data from their hospital. In hospitals randomized to implement the Bedside PEWS, the site-investigator will identify local educators and medical record administrators to the Bedside PEWS educators. They will collaborate to customize the Bedside PEWS documentation record. The site-investigator will assist in education of physicians at each site, and will help appoint the local Bedside PEWS Instructor who will assist with implementation.

3.3 Trial steering committee and data safety and monitoring committee (DSMC)

The DSMC will be comprised of a three members: a statistician, a senior clinician-administrator, and a clinician. After a brief teleconference meeting at the start of the study to establish internal process, the DSMC's role will be to review reports of study-associated adverse events provided by the Steering Committee. The DSMC will convene to review an Executive Steering Committee report describing the first 18 months of the study.

The Executive Steering Committee will meet 6-12 times per year throughout the study to discuss and resolve questions about the conduct of the study, to review site performance and (where required) will suggest remediation strategies. The Executive Steering Committee will report study-related adverse events to the DSMC. The Executive Steering Committee members have extensive practical and scientific expertise in resuscitation science, research methods, large clinical trials, multi-center registry and database management, program implementation and evaluation, biostatistics, health economics, health administration, guideline development, critical care, hospital and community paediatric hospital medicine and have published original research.^{1, 3, 4, 27, 36, 48, 49, 52, 58, 60-66} The steering committee is a strong collaboration of experienced resuscitation scientists, methodologists, educators, clinicians and administrators. In collaboration with the Canadian Critical Care Trials Group, and the clinicians and administrators of participating hospitals we have the expertise and momentum to successfully complete this clinically focussed, policy-relevant clinical trial to improve the outcomes of hospitalized children.

Table 1:
Scores and calling criteria to identify children at risk of near or actual cardiopulmonary arrest.

| Origin | Description | Development | ICU call threshold | AUC ROC |
|-------------------|--|--|--------------------------|---------|
| Bristol 2005 | 10 triggers plus +3 diagnosis related criteria + staff concern | Expert opinion Sens 99% Spec 63% | >1 criteria | 0.52 |
| Brighton 2005 | Score 0-11, 7 items | Expert opinion (Tucker 2009) Sens 71% Spec 91% | Score \geq 5 | 0.53 |
| Toronto 2006 | Score 0-26 9 static 7 dynamic | Delphi Consensus and statistical item selection Sens 78% Spec 95% | Score \geq 5 | 0.87 |
| Melbourne 2006 | 8 triggers + concern | Expert opinion No sens or specificity | \geq 1 criteria | 0.73 |
| Cincinnati 2007 | 4 subjective triggers + staff concern + parental concern | Expert review of local data No sens or specificity | \geq 1 criteria | NA |
| Baltimore 2008 | 8 subjective items 2 types of 'arrest' + concern | Expert opinion No sens or specificity | \geq 1 criteria | NA |
| Cardiff 2009 | Score 0-8 7 items | Expert Consensus Sens 70% Spec 90% | Score \geq 2 suggested | 0.62 |
| Bedside PEWS 2009 | Score 0-26 7 items | Expert opinion, statistical item reduction Sens 82% Spec 93% | Score \geq 8 | 0.87 |

Scores and calling criteria to identify children at risk for near and actual cardiopulmonary arrest. We evaluated the objective components in the dataset describing the 2074 patients in 4 paediatric hospitals. Limitations of the data to evaluate change of heart rate and respiratory rate more than 20 or 30 above 'baseline' were operationalized by using the mean for all control and case patients in each age range (<3m, 3-12months, 1-4 years, 5-12 years, >12 years) and looking for deviation from this number. The range (maximum-minimum) of the reported measurements of heart rate for each patient was more than 20 beats per minute in 86% of case and 40% of control-patients, and the range was more than 30 beats per minute in 74% of case and 22% of control patients. The range of reported Respiratory Rate Measurements was greater than 20 breaths per minute in 57% of case and 7% of control patients, and was more than 30 breaths per minute in 34% of case and 3% of control patients.

AUCROC= Area Under the Receiver Operating Characteristics Curve.

Table 2
Performance of the Bedside-PEWS score in 2074 hospitalized children

| Patient Category | Control patients | | Case patients | | p | AUCROC (95%CI) |
|---------------------------------|------------------|--------------------|---------------|--------------------|--------|------------------|
| | N | Score Median (IQR) | N | Score Median (IQR) | | |
| All | 1388 | 2 (1-4) | 686 | 8 (5-12) | <.0001 | 0.87 (0.85-0.89) |
| Urgent ICU | 772 | 2 (1-4) | 381 | 10 (7-13) | <.0001 | 0.92 (0.90-0.94) |
| Code Blue | 616 | 2 (1-4) | 305 | 6 (3-10) | <.0001 | 0.81 (0.78-0.84) |
| Age | | | | | | |
| <3 months | 333 | 2 (1-4) | 190 | 7 (4-10) | <.0001 | 0.83 (0.79-0.86) |
| 3-<12 months | 362 | 2 (1-4) | 164 | 8 (6-11) | <.0001 | 0.86 (0.82-0.90) |
| 1-<5 years | 286 | 2 (1-4) | 134 | 9 (5-13) | <.0001 | 0.90 (0.87-0.93) |
| 5-12 years | 221 | 2 (1-3) | 110 | 10 (5-13) | <.0001 | 0.89 (0.84-0.93) |
| >12 years | 186 | 3 (2-4) | 88 | 11 (6-14) | <.0001 | 0.91 (0.87-0.95) |
| Hospital | | | | | | |
| 1 | 658 | 2 (1-4) | 324 | 9 (6-12) | <.0001 | 0.88 (0.85-0.90) |
| 2 | 478 | 1 (1-3) | 238 | 6 (4-9) | <.0001 | 0.89 (0.86-0.92) |
| 3 | 164 | 5 (2-6) | 80 | 12 (9-15.5) | <.0001 | 0.91 (0.87-0.95) |
| 4 | 88 | 2 (1-3) | 44 | 9 (4-12) | <.0001 | 0.89 (0.83-0.96) |
| Chronic Disease | | | | | | |
| Transplant | 73 | 2 (1-3) | 58 | 11 (7-12) | <.0001 | 0.94 (0.90-0.98) |
| Heart Disease | 386 | 3 (2-5) | 233 | 8 (6-11) | <.0001 | 0.84 (0.81-0.88) |
| Severe Cerebral Palsy | 34 | 2 (1-4) | 62 | 10 (7-13) | <.0001 | 0.92 (0.86-0.98) |
| Medical Device | | | | | | |
| Tracheostomy | 36 | 4 (1.5-5.5) | 57 | 7 (4-11) | <.0001 | 0.76 (0.67-0.86) |
| Feeding Tube | 112 | 3 (1-5) | 138 | 10 (6-13) | <.0001 | 0.86 (0.82-0.91) |
| Home Oxygen | 27 | 5 (2-7) | 47 | 8 (6-11) | <.0001 | 0.79 (0.69-0.90) |
| Acute condition | | | | | | |
| Seizures>15 min | 6 | 2 (2-4) | 47 | 6 (3-10) | 0.1146 | 0.74 (0.48-0.99) |
| Complexity | | | | | | |
| >3 services | 136 | 3 (1-5) | 164 | 9 (6-12) | <.0001 | 0.87 (0.83-0.91) |
| >10 medications/day | 109 | 3 (2-5) | 162 | 10 (6-13) | <.0001 | 0.85 (0.81-0.90) |
| Administrative | | | | | | |
| Recent primary service transfer | 5 | 1 (0-2) | 18 | 7 (3-8) | 0.0040 | 0.89 (0.75-1.00) |

IQR= Interquartile range. The hospitals are Hospital for Sick Children, Birmingham Children’s Hospital, Stollery Children’s Hospital and Ste. Justines Hospital. AUCROC= Area Under the Receiver Operating Characteristics Curve.

Table 3

Systematic Review: methods to identify children at risk for near & actual cardiopulmonary arrest

In order to identify published scores and calling criteria not known to the applicants, we modified and re-ran the search used in the development of our original PEWS score with the assistance of an Academic Librarian.

The following comprehensive search strategy was run in Ovid MEDLINE(R) 1950 to Present with Daily Update (updated to September 8, 2009) using the following search terms. A total of 1,069 references were retrieved.

| | |
|--------|---|
| Source | Ovid MEDLINE(R) 1950 to Present with Daily Update |
|--------|---|

| Set # | History | Comment |
|-------|--|--|
| 1 | (Early adj2 Warning adj2 (Score* or system* or track* or trigger*)).ti,ab. or (pews or ews or mews).ti,ab. or ((inhospital or "in-hospital") adj2 (cardiac or heart or cardiopulmonary or respiratory) adj2 arrest:).ti,ab. | Early warning system textword terms |
| 2 | critical illness/ or critical care/ or severity of illness index/ or diagnosis-related groups/ or (severity adj 5 illness).ti,ab. or ((inhospital or "in-hospital") adj2 (cardiac or heart or cardiopulmonary or respiratory) adj2 arrest:).ti,ab. | Subject heading and textword search terms for patient population |
| 3 | emergency medical services/ or emergency service, hospital/ or ((pediatric or paediatric) adj2 medical adj2 emergency adj2 (team or teams or system* or service*)).ti,ab. or (rapid adj2 response).ti,ab. | Subject heading and textword search terms for emergency response terms |
| 4 | 1 or (2 and 3) | Base search set |
| 5 | limit 4 to "all child (0 to 18 years)" | Age group limit |

This search was re-run in the Cochrane Database of Systematic Reviews and identified 4 reviews, of which one was relevant. Courtesy of Ms E Uleryk, Academic Librarian, Hospital Library, The Hospital for Sick Children.

References were downloaded to Endnote (version X Thomson, www.endnote.com) and reviewed by the PI (Parshuram). One additional reference describing the Brighton Score was identified. This was included in the background review. Reference 102: Adshead and Thomson. Use of a paediatric early warning system in emergency departments. 2009 Emergency Nurse Volume 17 (1) pages 22-25.

Table 4

Intervention Hospitals: Implementing the Bedside Paediatric Early Warning System:

Implementation will be conducted in 7 phases beginning with modifications of the system to comply with local preferences and formal requirements, and culminating in clinical application. As we have conducted previously.

| # | Phase timeframe | Description |
|---|---|--|
| 1 | Meeting Local Documentation Standards 4-8 months before implementation | Paper documentation: Modification to meet local requirements for paper size, punched-hole placement, bar coding, hospital and patient identifiers, certification that the quality of photocopied Bedside PEWS documentation records meets local standards, certification of paper quality, and local health-records approval. Electronic health records (EHR) documentation: Modification of the electronic format to meet local requirements for screen size and resolution, local printing requirements (appearance, hospital logo/identifier, bar coding), installation by local information services staff, including establishment of the interface between existing EHR, pilot testing for overall functionality, and local health-records approval. Implementing sites with EHR will also develop an explicit plan for documentation during ‘down-time’ of the local electronic health record. |
| 2 | Matching the Score Matched Care Recommendations to the local vernacular 4-8 months before frontline staff education | Modification of the appropriate (community, referral hospital) score-matched care recommendations to the local vernacular. For example in a hospital where the ICU team may be called ‘RACE’ the recommendations would read ‘consider referral to the RACE team’. Following local confirmation, the modified score-matched care recommendations will be printed on the Bedside PEWS clipboards, pocket cards and the documentation record (paper and electronic format). |
| 3 | Bedside PEWS Instructor Course 2-4 months before frontline staff education | Implementation teams from each implementing site, comprised of Nurse Educators (or equivalents), and the physician lead will attend this 2-day course conducted by the Bedside PEWS Educators and the PI, in the Learning Institute at the Hospital for Sick Children (See letter of support). The course objectives are: [1] Demonstration of technical competence with the Bedside PEWS. [2] Familiarity with the Bedside PEWS frontline education program and materials. [3] Description of the implementation environment and articulation of an implementation plan customized to local requirements [4] Establishment of a post-course timetable for weekly communication with the Bedside PEWS Educators. |
| 4 | Articulating the site-specific plan (Frontline staff education & Clinical implementation 1-3 months before frontline staff education | This written plan will be articulated by the site Bedside PEWS Instructors, and will include: [1] Schedules for meetings with frontline staff (formal, informal) [2] Milestones for training (numbers of successfully trained individuals), completion of initial training, and the date of clinical implementation. [3] A post-implementation ‘maintenance’ strategy. [4] A weekly reporting plan. [5] Identification of the area in which the implementation run-in will occur. |

| | | |
|---|--|--|
| 5 | <p>Frontline staff education Beginning 3 months before run-in clinical implementation</p> | <p>This 4 hour training session for frontline staff (registered nurses and respiratory therapists) will be scheduled over the 3 months preceding clinical implementation. Each session will include 2 hours of small-group (6-8 person per educator) education sessions, and 2 hours of interactive use of the Bedside PEWS documentation record.</p> <p>Physicians will attend a 90 minute session explaining the Bedside PEWS and its clinical application. Sessions will be conducted by the Bedside PEWS Instructors, and the Physician Site Lead.</p> |
| 6 | <p>Run-in Clinical Implementation 5 weeks before Hospital-wide implementation</p> | <p>Implementation will occur in a pre-identified ward area with 20 or more beds. This focussed implementation will begin 5 weeks before hospital-wide implementation. This focussed implementation will provide local experience, identification of implementation challenges, and pre-emptive application of solutions gathered from the experience locally, of the Bedside PEWS team, and of other sites.</p> |
| 7 | <p>Hospital-wide Implementation</p> | <p>The go-live date will be approved by hospital administrative and clinical leads and will be supported by the Bedside PEWS educator team. A teleconference will be scheduled one week after implementation to discuss the first week of implementation, and for advice from the Bedside PEWS team (Educators and PI). Each teleconference session will be recorded for later review.</p> |

Table 5

Secondary Outcomes: Clinical Deterioration Events & Significant Clinical Deterioration Events (SCDE)

| | Definition | SCDE |
|-----------------------------------|---|------|
| [1] Early Transfer | <60ml/kg intravenous or intraosseous fluid resuscitation given in the 12 hours before transfer, No intravenous or intra-osseous inotrope or Vasoactive medications and no Positive Pressure Ventilation (Bag-mask or Endotracheal) in the 12 hours before transfer. | No |
| [2] Intermediate Transfer | [2] Non-Invasive Respiratory = Positive pressure ventilation in the 12 hours before transfer, but not intubated at the time of transfer. This category includes children receiving mask delivered Positive Airway Pressure at any stage in the 12 hours before transfer and at the time of transfer. Mechanical ventilation during anaesthesia for a scheduled procedure is not included. | No |
| [3] | [3] Respiratory = intubated and, or receiving endotracheal ventilation at the time of transfer, or intubated within one hour of PICU admission. | Yes |
| [4] | [4] Circulatory = >60ml/kg intravenous or intraosseous fluid resuscitation given in the 12 hours before transfer, and administration of any intravenous or intra-osseous inotrope or vasopressor ¹⁸ administered at the time of transfer or at any stage in the 12 hours preceding transfer. Patients in this category can include positive pressure ventilation [2]. | Yes |
| [5] Late Transfer | Respiratory [3] <i>and</i> Circulatory [4] support before transfer. | Yes |
| [6] Cardiopulmonary Resuscitation | Chest compressions before transfer from ward area or within one hour of PICU admission or ECMO instituted before or within one hour of PICU admission. | Yes |
| [7] Death | Death on an inpatient ward, other than in those patients with DNR orders. Death may occur despite CPR (or intention to perform CPR if patient is pronounced dead without CPR). No transfer from ward area. | Yes |

Transfer is when a patient is urgently transferred to a paediatric intensive care unit (PICU) in the participating hospital. The time of transfer is the arrival in the PICU. Urgent means departure from the inpatient ward in <6 hours from the time the transfer was initiated. When a patient is urgently admitted from an eligible hospital ward to a PICU via a procedure in the OR, the time of transfer to 'PICU' is regarded as beginning at the time of transfer (departure from the inpatient ward) to the operating room. Treatments other than cardiopulmonary resuscitation provided in the operating room are not included in the calculation of the Clinical Deterioration Event. Unexpected events occurring in the operating room that require post-operative / post-anaesthetic care in the PICU, in patients who were not anticipated to require PICU will at the time the patient was transferred from the inpatient ward will not be regarded as clinical deterioration events.

A **PICU** is defined as an area with dedicated facilities for mechanical ventilation, circulatory support and invasive circulatory and respiratory monitoring (for example with arterial and central venous pressure monitoring). Other areas designated for patients of increased acuity, such as 'constant observation' or 'high dependency' or 'step-down' units will be regarded as part of the PICU where the PICU staff physicians are wholly or jointly responsible for the care of children in these areas (can write orders in the chart). Routinely admitted patients will include children outside the neonatal period who are <12 years of age at admission.

ECMO is Extracorporeal Membrane Oxygenator Therapy.

Table 6

Abstraction to evaluate the potential preventability of cardiac arrest.

| | |
|------------------------------------|--|
| Age | In months if less than 1 year, otherwise in years |
| Diagnoses Primary and Secondary | Diagnoses represent active problems or a treated problem. Primary = the main diagnosis Secondary = clinically relevant but less relevant than the overarching main diagnosis. See Case Report form |
| Severity of Illness | 1 home oxygen 2 tracheostomy 3 percutaneous – enteral feeding tube 4 permanent vascular access central line 5 permanent vascular access other than central line 6 Arterial line in-situ 7 PICU discharge (during this hospitalization) in last 2 days, >2 days or no ICU admission during this hospitalization (includes NICU admission). 8 Length of hospital stay before event: <1 week, ≥ 1 week 9 previous cardiac arrest (in this hospital admission). |
| Recent procedures | Procedures. (indicate all that apply) In the last 7 days... 1 Cardiac – with cardiopulmonary bypass 2 Cardiac – without cardiopulmonary bypass 2 Cardiac – catheterization 3 Vascular (includes major endvascular procedures, open surgery) 4 Vascular – insertion / removal of permanent vascular access 5 Central Nervous System 6 Spinal / other neurologic-orthopaedic surgery 7 Craniofacial 8 Orthopaedic (not spinal) 9 Ear Nose and Throat 10 Thoracic (not cardiac or vascular) 11 Abdominal surgery 12 Dental 13 Plastic / Cutaneous and, or muscular 14 Ophthalmologic Surgery A Free Text Primary Procedure B Free Text Secondary Procedure 1 C Free Text Secondary Procedure 2 |
| Acute Problems | 1 Seizures 2 CNS other 3 ENT 4 Respiratory |

| | |
|--------------------------|---|
| | <p>5 Circulatory 6 Renal 7 Hepatic</p> <p>A Free Text description</p> |
| Medications | List of medications given in the 25 hours before the event and the hour in which they were administered. |
| Vital Signs | From 13 hours before event until time of event: Documented Heart Rate, Respiratory Rate, Systolic Blood Pressure, Diastolic blood pressure, Trans-cutaneous oxygen Saturation, Capillary Refill Time, Respiratory Effort, Temperature, Level of Consciousness (Glasgow Coma Scale, Comfort scale) pupil size. |
| Respiratory Intervention | From 13 hours before event until time of event: Documented Oxygen therapy Nebulized therapy Positive pressure ventilation |
| Circulatory Intervention | From 13 hours before event until time of event: Documented Intravenous Fluid therapy (total fluids input) expressed in ml /kg averaged over each hour Transfusion VasoActive Agents (as yes / no) : Dopamine, Milrinone, Amrinone, NorEpinephrine, Epinephrine, Prostaglandin Urinary output |
| Investigations | <p>Two most recent sets of blood results if drawn in the last 48 hours.</p> <p>For each of the following laboratory investigations: we will record the value</p> <p>[a] closest to 48 hrs before and >24 hours before</p> <p>[b] closest to 12 hrs before AND <24 h & >12 h before event</p> <p>[c] closest to one hr before AND <12 h & >1hr before event</p> <p>[d] number of tests of the specified type assessed <24 h & >1 h before event</p> <p>[e] are relevant upper and lower limit of normal for the test</p> <p>Inflammatory Markers: C-Reactive Protein, Erythrocyte Sedimentation Rate, Procalcitonin.</p> <p>Full Blood count: Haemoglobin, White Cell Count, Bands, Platelet Count</p> <p>Electrolytes: Sodium, Potassium, Calcium (total), Calcium Ionized, Magnesium</p> <p>Blood Gas arterial: PaO₂, PaCO₂, HCO₃ (measured, calculated), pH.</p> <p>Blood Gas mixed venous: PaO₂, PaCO₂, HCO₃ (measured, calculated), pH.</p> <p>Metabolic: Ammonia, Lactate (not peripheral) Glucose,</p> <p>Liver Tests: Aspartate and Alanine Aminotransferase, Bilirubin (conjugated, and un-conjugated), Lactate Dehydrogenase, International Normalized Ratio (INR), Partial Prothrombin Time.</p> |
| Radiology | <p>Chest XRay in 48 hours before event: not done / new or worsening infiltrates- abnormality / unchanged / normal.</p> <p>Neuroimaging in 48 hours before event: not done / lesion new or expanding / normal / unchanged</p> <p>Echocardiogram in 48 hours before event: not done / deteriorating cardiac function / improving cardiac function / normal function / unchanged.</p> |

| | |
|---------------------|--|
| Infection | From samples taken in the 96 hours before event: Confirmed Positive Blood Culture: Yes / no and list organism Positive Microbiologic Specimen from other site 1 CNS 2 Respiratory Tract 3 Urine 4 Drain – other (specified) Confirmed positive cultures are judged not to be contaminants by the reporting site investigator. |
| Other relevant data | Short < 300 word summary (clinical data referenced to event time, no patient identifiers) |

Legend

Items to be documented for clinical deterioration events that include a cardiac arrest (scale rating 4 or 5). After abstraction items will be reviewed by the site investigator, and submitted anonymously to the data coordinating center. The data will then be presented in a standard format – including the use of the Bedside PEWS documentation record – for evaluation of preventability by a multi-disciplinary adjudication panel.

Table 7

Preventability criteria

| Rating | Category |
|--------|---|
| 1 | Virtually no evidence of preventability |
| 2 | Slight to modest evidence of preventability |
| 3 | Preventability not quite likely (less than 50/50, but “close call”) |
| 4 | Preventability more than likely (more than 50/50, but “close call”) |
| 5 | Strong evidence of preventability |
| 6 | Virtually certain evidence of preventability |

Legend

Preventability criteria, as used in the Canadian Adverse Events Study. A rating of 4 or more was regarded as a high degree of preventability.¹²⁶

Appendices

1 Power & Sample Size

2 Case Report Form- see separate attachment

Power & Sample Size Appendix

Power Calculations were determined using Hayes RJ, Bennett S: Simple sample size calculation for cluster-randomized trials. Int J Epidemiol 1999; 28: 319-26. Reference 129.

[1] All Cause Hospital Mortality

Baseline rate data are presented from participating hospital. We estimate that this study will have sufficient power to demonstrate 18% relative risk reductions in all cause mortality this corresponds to an absolute risk reduction of 0.9%.

Baseline Data

| Participating Paediatric Hospital | All Cause Mortality / 1000 discharges |
|--|---------------------------------------|
| The Hospital for Sick Children | 2.17 |
| BC Children's Hospital | 5.0 |
| John Hopkins Hospital | 5.08 |
| Stollery Children's Hospital | 6.8 |
| St Justine Children's Hospital | 2.1 |
| McMaster Hospital | 8.4 |
| Children's Hospital of Eastern Ontario | 7.22 |
| Centre Mere-Enfant du CHUQ | 2.07 |
| London Health Sciences Center | 6.98 |
| South Eastern Ontario Health Sciences Centre | 7.0 |
| St George's Hospital | 4.46 |
| Children's Medical Center Dallas | 6.5 |
| IWK Health Centre | 2.31 |
| Alberta Children's Hospital | 5.4 |
| Overall Average Rate | 5.11 |

Reference: Feudtner 2009 (Reference #108)

8 year cohort

Pennsylvania hospitals from 1994-2001

[includes Referral and Community Hospitals]

678,365 subjects

2,202 deaths during hospitalization 3.2

Analytic Method: Logistic regression

| Relative Risk Reduction | Baseline Rate |
|-------------------------|-------------------------------|
| 0.178 | 5.1 / 1000 discharges. |
| 0.199 | 3.2 / 1000 discharges |
| | |

Assumptions: n=20 hospitals: alpha=0.05, z=1.96, power=80%, average bed size=119.85, length of stay=4, 0.90 average occupancy, k=0.15.

[2] Significant Clinical Deterioration Events in four major paediatric referral hospitals in 2007-8

| | | |
|---|---------------------|---|
| Hospital Admissions | 55963 | |
| PICU Beds | 62 | |
| PICU Discharges | 7300 | |
| Unplanned PICU Admits | 1052 14.5% 18 | N /PICU Discharges /1000 Hospital Discharges |
| PICU Mortality following Unplanned Admits | 65 6.2% 1.2 | N /Unplanned Discharges /1000 Hospital Discharges |
| Total Code Blue Events | 150 3 0.75 | N /1000 Hospital Discharges /1000 Patient Days |

Data are from The Ontario Paediatric Critical Care Response Team Collaborative report (Kotsakis 2009). They represent 2 years of data from the four largest paediatric referral hospitals in Ontario. In the two years following 31 January 2007, there were 55963 Hospital Discharges, 1052 Urgent PICU admissions, and 150 Code Blue events (after the introduction of MET-RRT at each site). ICU mortality was overall 6.2% following urgent ICU admission – lower than the 15.1% in our single center data from an earlier era.

Assuming an average hospital length of stay of 4 days (397,556 patient days /99,389 discharges – data from participating referral hospitals), we estimate a rate of SCDE of 2/1000 patient days. With 20 sites we will be able to show a 31% reduction in significant clinical deterioration events (80% power, alpha=0.05, k= 0.15). This corresponds to an absolute risk reduction of 0.62 events per 1000 patient days.

[3] Code Blue Events

These immediate calls for medical assistance from a resuscitation team occur at a rate of 0.75/1000 Patient Days. With this rate the maximum relative risk reduction that can be shown with 20 referral hospitals is 0.41 (alpha=0.05, z=1.96, power=80%, an average bed size of 119.85, a length of stay of 4, k=0.15.) This is an absolute risk reduction of 0.3/1000 events per thousand patient days.

[4] Stat Calls

Method: Poisson regression

Preliminary Data 8.13 stat calls per 1000 patient days at the Hospital for Sick Children. The maximum relative risk reduction that can be shown is 0.181 (alpha=0.05, z=1.96, power=80%, an average bed size of 119.85, a length of stay of 4, k=0.15, n=20, baseline rate=8.13 per 1000 patient days). This corresponds to an absolute risk reduction of 1.45 calls per thousand patient days.

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