BMJ Open

Establishment of a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005803
Article Type:	Protocol
Date Submitted by the Author:	29-May-2014
Complete List of Authors:	Denney, Joshua; Johns Hopkins University, Division of Pulmonary and Critical Care Capanni, Francesca; Johns Hopkins University, Division of Pulmonary and Critical Care Herrera, Phabiola; Johns Hopkins University, Division of Parasitic Diseases Dulanto, Augusto; Johns Hopkins University, Division of Pulmonary and Critical Care Roldan, Rollin; ESSALUD, Servicio de Cuidados Intensivos Paz, Enrique; ESSALUD, Servicio de Cuidados Intensivos Jaymez, Amador; MINSA, Servicio de Cuidados Intensivos Chirinos, Eduardo; MINSA, Servicio de Cuidados Intensivos Portugal, Jose; ESSALUD, Servicio de Cuidados Intensivos Quispe, Rocio; ESSALUD, Servicio de Cuidados Intensivos Brower, Roy; Johns Hopkins University, Division of Pulmonary and Critical Care Checkley, William; Johns Hopkins University, Division of Pulmonary and Critical Care
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY, Thoracic medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

Establishment of a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru

Joshua A Denney (1), Francesca Capanni (1), Phabiola Herrera (1), Augusto Dulanto (1), Rollin Roldan (2), Enrique Paz (3), Amador A Jaymez (4), Eduardo E Chirinos (5), Jose Portugal (2), Rocio Quispe (2), Roy G Brower (1), William Checkley (1, 6); INTENSIVOS Cohort Study.

1. Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, USA.
2. Servicio De Cuidados Intensivos, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.
3. Servicio De Cuidados Intensivos, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru.
4. Servicio De Cuidados Intensivos, Hospital Nacional Arzobispo Loayza, Lima, Peru.
5. Servicio De Cuidados Intensivos, Hospital De Emergencias José Casimiro Ulloa, Lima, Peru.
6. Program in Global Disease Epidemiology and Control, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Corresponding author:

William Checkley MD, PhD

Division of Pulmonary and Critical Care

School of Medicine

Johns Hopkins University

1800 Orleans Ave Suite 9121

Baltimore, MD 21205

Email: wcheckl1@jhmi.edu

Telephone: 443-287-8741

.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ABSTRACT

Introduction: Mechanical ventilation is a cornerstone in the management of critically ill patients worldwide; however, less is known about the clinical management of mechanically ventilated patients in low- and middle-income countries (LMICs) where limitations of resources including equipment, staff and access to medical information may play an important role in defining patient-centered outcomes. The purpose of this article is to present the design of INTENSIVOS, a prospective, longitudinal study of mechanically ventilated patients in Peru.

Methods and Analysis: We outline methods employed to characterize a prospective cohort of patients receiving at least 24 hours of invasive mechanical ventilation in five Peruvian ICUs and one ICU in the United States. Primary outcomes include 90-day mortality, time on mechanical ventilation, hospital and ICU length of stays, and prevalence of ARDS. We also describe structure and process variables across the different ICUs. Average annual ICU mortality in the five Peruvian ICUs was 19.6% (SD=2.4%), similar to in the ICU in the United States (19%). Differences in structure- and process-related factors between the Peruvian ICUs and that in the United States include lack of respiratory therapists, no multidisciplinary rounds, no electronic patient records or computerized order entry, and absence of standardized protocols in the former.

Ethics and Dissemination: We obtained ethics approval at each of the four participating hospitals in Lima, Peru and at the Johns Hopkins School of Medicine, Baltimore, USA. We identified important differences in structure- and process-related factors between participating ICUs in Peru and the United States. In subsequent analyses, we aim to identify interventions tailored to resource-limited settings that may result in improved patient-centered outcomes.

Keywords: ICU, Critical Care, Outcomes, Protocols, ICU organization

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Mechanical ventilation has become a mainstay of therapy in the care of critically-ill patients. Intensive care unit (ICU) practices, mechanical ventilation strategies and their societal costs in high-income countries (HIC) are well documented. For example, in Germany, Chalfin (1) calculated that ICU care comprised 20% of hospital costs. In the United States, Wunsch *et al.* projected that 3% of inpatient hospitalizations required mechanical ventilation in 2005, comprising 30% of all ICU admissions and accounting for a disproportionate 12% of all hospital costs (2). Factors contributing to a higher cost of an individual ICU stay include sepsis and initiation of mechanical ventilation. (3, 4) Despite the higher cost and quality of care that an ICU setting implies, mortality remains high. In the United States, studies show that approximately 30% of all patients requiring mechanical ventilation die before ICU discharge (2). A Finnish study estimated a one-year mortality rate of 35% for patients receiving more than 6 hours of continuous mechanical ventilation (5).

In resource-limited settings, however, less is known about clinical practices and mechanical ventilation strategies used in critically-ill patients (6). Moreover, the burden of critical illness is higher than generally perceived in low- and middle-income countries (LMICs), and it is expected to increase with an aging population (6, 7). Esteban *et al.* analyzed data from 361 ICUs in 20 countries across the Americas and Europe and showed a statistically significant mortality difference between the United States, European, and Latin American ICUs for all patients receiving mechanical ventilation within a one month period, i.e., 27% vs. 31% vs. 34%, respectively (8). Their analysis demonstrates that disparities in mortality rates in ICUs of varying geographical and socioeconomic status exist, but did not address what factors may be

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

contributing to these differences (8). Furthermore, the results from Latin America aggregate data from countries of varying wealth, which may mask higher mortality rates in poorer settings.

ICUs with fewer resources and greater economic limitations may have essential differences in delivery of critical care with resulting variations in patient-centered outcomes. These disparities and their effect are not well understood (6, 9, 10). Implementation of proven ICU protocols can reduce both mortality and costs (9). Process-driven interventions, such as standardized protocols of care, could potentially play a large role in minimizing costs while improving patient outcomes which could be especially advantageous in resource-limited settings (6, 9). Our study focuses on critically-ill patients receiving mechanical ventilation in LMICs with significant resource limitations. Our goal is to better understand best practices in resource-limited settings.

The purpose of this article is to present the design of INTENSIVOS, a prospective, longitudinal study of mechanically ventilated patients in Lima, Peru. In 2009, Peru spent 5% of its gross domestic product on healthcare versus 16% in the United States and a median of 10% across European countries (12). The role of intensive care and mechanical ventilation will become increasingly important. In this study, we characterize clinical and ventilator management of patients requiring a minimum of 24 hours of mechanical ventilation in five ICUs in public hospitals in Peru and one ICU in an academic medical center in the United States. We hypothesize that measurable differences in patient-centered metrics such as mortality and length of stay exist between the ICUs in LMICs and the United States. As comparing healthcare systems internationally can be difficult due to variations in admission criteria, practice and management, we will adjust mortality by severity of illness upon starting mechanical ventilation using commonly accepted severity scores and will enroll patients that receive ICU care within a

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

48-hour window of starting mechanical ventilation. The ultimate goal of the study is to identify best practices and standardized care tailored to resource-limited settings that will result in improved patient-centered outcomes and lower costs.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS

Study Objectives

We seek to characterize 90-day mortality, time spent on mechanical ventilation, ICU and hospital length of stay, mechanical ventilation strategies and selected aspects of clinical management of critically-ill patients requiring at least 24 hours of invasive mechanical ventilation in five ICUs in Lima, Peru and in one ICU in the United States (Figure 1). We further seek to characterize the proportion of patients admitted to the ICU with acute respiratory distress syndrome (ARDS) and the proportion of patients who will develop ARDS while in the ICU. Finally, we will utilize ICU prognostic scores to stratify patients by severity of illness and compare mortality rates of critically ill patients with those of similar illness severity in concurrent cohorts of ICU patients in the United States, including the one collected in this study and in publicly-available datasets. Primary outcomes for this study will be 90-day mortality, time on mechanical ventilation, ICU and hospital length of stays, and prevalence of ARDS.

Study Design

This is a prospective, longitudinal study. At enrollment, we obtained demographics, chronic disease and acute physiological data for all patients meeting eligibility criteria. We then followed patients daily to monitor vital status, clinical and ventilator management, acute physiology and use of sedation during their ICU stay for up to 28 days in the ICU, until ICU discharge or death. Patients who were successfully discharged from the ICU were followed for vital status during their inpatient hospital stay. All patients were contacted at 90 days after enrollment to assess vital status. Survivors in Peru only will be contacted again at 6, 12, 24 and 60 months (long-term outcomes) after enrollment into the study to assess for vital status. A subset of survivors will be

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

asked to participate in an ancillary study and undergo a battery of tests at follow-up, including: questionnaires of quality of life, respiratory symptoms, anxiety, depression and post-traumatic stress disorder; and, clinical tests including a six-minute walk test, pulmonary function testing and handgrip strength.

We obtained Institutional Review Board (IRB) approval at each of the four participating hospitals in Lima, Peru: Hospital Nacional Edgardo Rebagliati Martins, Hospital Nacional Guillermo Almenara Irigoyen, Hospital Nacional Arzobispo Loayza and Hospital de Emergencias Casimiro Ulloa. In the United States, IRB approval was obtained from the Johns Hopkins School of Medicine, Baltimore, USA. All IRBs provided a waiver of consent for this study.

Eligibility criteria

Eligibility criteria include: 1) age ≥18 years, 2) at least 24 hours of invasive mechanical ventilation in one of the ICUs participating in the study and 3) enrollment into the study within 48 hours of onset of mechanical ventilation.

Study Sites

The study was conducted in five ICUs at four public hospitals of the Social Security System (ESSALUD) and Ministry of Health (MINSA) in Lima, Peru; and, in the Medical Intensive Care Unit (MICU) of Johns Hopkins Hospital (Figure 2). We invited only one ICU per hospital with the exception of Hospital Rebagliati, for which we included two ICUs. Participating ICUs were selected on the basis of high case volume and willingness to participate. A four-week test period was initially carried out at each hospital in Peru to determine feasibility and monthly case

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

volume. Of six hospitals approached in Peru, two were unable to meet established *a priori* requirements during the test period and were not invited to continue in the study.

Study team

We organized data collection and quality control using a tiered approach. At each ICU, we identified a team of 2 to 7 study nurses who were responsible for paper-based data collection on a daily basis and an ICU physician (co-investigators) who supervised data collection and who were responsible for data quality, review of clinical and ventilator data and interpretation of chest X-rays (CXR). In addition, a team of two study physician coordinators from the Clinical and Data Coordinating Center (DCC) oversaw the day-to-day operations of the study and act as liaisons between the principal investigator and co-investigators. The DCC is composed of team members located both in Peru and the United States. Study physician coordinators visited each ICU on average two to three times a week to verify data accuracy and fidelity along with co-investigators and study nurses, perform range checks and obtain an electronic copy of CXRs. Incomplete or incorrectly entered case report forms (CRFs) were returned to study nurses for revision of missing or flagged data. Data forms were collected from all ICUs on a weekly basis and transferred to the DCC office in Peru for double data entry to a centralized database. The DCC data manager also conducted a careful review, and incomplete or incorrectly entered CRFs were returned to the study physician coordinators, who reviewed missed or flagged data with co-investigators and study nurses. Finally, a DCC nurse was responsible for follow-up telephone calls to assess vital status after hospital discharge and invited participants to join the long-term outcomes ancillary study among survivors.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Case Report Forms

CRFs were modeled after forms used by ARDS Network trials with additional fields added to capture the Charlson comorbidity index (13), APACHE II (14), APACHE III (15), MODS (16), Mortality Probability Model III (17) and SOFA scores (18). The CRFs were designed to capture demographics and chronic health information at baseline and daily information on acute physiology, selected aspects of clinical management, mechanical ventilation and weaning practices, and sedation management. Forms were originally written in English, translated into Spanish and then back-translated into English to confirm accuracy of translation.

Study team members at participating hospitals reviewed and tested Spanish CRFs during the pilot phase. During this pilot, differences in ICU practices between the United States and Peruvian ICUs became apparent and the CRFs were modified to accommodate differences. For example, resource limitations at participating ICUs in Peru limit laboratory data collection to a maximum of once per day per patient, with data frequently being collected less than once per day. Moreover, laboratory tests are usually individually ordered rather that in order sets. Likewise, CXRs are ordered less frequently than in ICUs in the United Status.

Prior to study start, the study team underwent an in-person training session on how to accurately record data in paper-based CRFs. In-person training sessions were repeated approximately every six months during the first two years. All study team members were provided with a manual of operations with instructions on how to accurately fill the forms. These forms were completed in black or blue ink, reviewed by co-investigators and study physician coordinators and then transferred to the DCC where they were double data entered into a centralized database. The CRFs are composed of four parts: a Patient Contact Form (PCF), Baseline Clinical Information Form (BCI), Daily Clinical Information Form (DCI), and a Study

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Termination Form (STF). Paper-based worksheets to calculate ICU severity scores such as APACHE II (A2F), APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA (SOF) were also provided to the study team. Two additional forms were added later into the study and will be available in a subset of study participants: ARDS Follow-up Form (AFF), in which study team members recorded additional ventilator parameters during the first 7 days after onset in patients that met criteria for ARDS; and, Sepsis Evaluation Form (SEF), which recorded additional clinical parameters associated with sepsis during the first 14 days after enrollment.

The PCF included patient information such as name, date of birth, address and telephone contact information for determination of follow-up of vital status after hospital discharge. This is the only form that contained protected patient information linked to a corresponding unique participant identification code (PID) in the study. The PCFs are stored in locked cabinets, and the electronic database is only available to the DCC data manager and to the nurse in charge of follow-up telephone calls. To complete subsequent forms pertaining to a specific patient, the PID was transcribed exactly as it appeared on the PCF. PIDs were checked daily by ICU team members for verification of their accuracy. The PCFs for individual patients serve as the only link between medical information and patient identifying information, and will be destroyed upon completion of the study.

The BCI was completed upon patient admission to the ICU. If a patient was readmitted to the ICU, a new BCI was filled. The BCI collected information in the first 24 hours of mechanical ventilation The BCI also recorded height, chronic health information and acute physiology data. Height was measured following a standardized approach while in supine position. The BCI also had screening criteria for ARDS modeled after that used by the ARDS Network to assess whether or not a patient had ARDS upon enrollment.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The DCI was collected daily, considering day 0 as the first 24 hours of mechanical ventilation. It consisted of daily laboratory tests, selected aspects of clinical management, mechanical ventilation management, and use of medications such as steroids, sedatives and antibiotics. DCIs were completed daily for the first 28 days or until patients died or was discharged from the ICU. Data for the DCI was captured over a defined 24-hour period of time. To ensure that data was captured only once it was necessary to create an arbitrary 24-hour period (i.e., a study day). A study day was defined as the 24 hours prior to 8 A.M. on the day of data collection. Participating hospitals will be instructed to enter data for each DCI using values obtained as close as possible to 8 A.M.

The STF was used to record 90-day mortality and other ICU milestones such as time on mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-hospital deaths were also recorded. Patients were followed throughout their hospital stay after ICU discharge to determine date of hospital discharge or death. Vital status was assessed in the STF at 15, 30, 45, 60 and 90 days after initiation of mechanical ventilation. After hospital discharge, vital status was obtained via a telephone call at 90 days and at subsequent dates as part of the long-term outcomes sub-study.

Although participating ICUs in Peru are in the process of acquiring the necessary infrastructure for electronic medical records, none currently have it in place. Thus, data collectors manually recorded all data in paper-based forms. Although the CRFs had a section to record CXR findings, digital copies of all corresponding CXR were also obtained and stored.

Sample size

The study spanned a period of three years. We aimed to enroll at least 300 patients at each participating ICU for a total of 1800 participants across all six ICUs. To detect a difference in

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

90-day mortality of 10% between a Peruvian ICU and the Johns Hopkins MICU with an expected baseline mortality of 30%, confidence level of 95% and power 90%, we estimated that we would need 240 participants per ICU. We chose to over-enroll by 20% to account for potential missing data.

Characteristics of participating ICUs

The five Peruvian ICUs that took part in this study were hosted in four public Peruvian hospitals of varying size and sources of funding, and thus there are some differences between the number of beds and influx of patients between units (Table 1). The Hospital Rebagliati, site of two participating ICUs, is the largest center with over 1,500 beds and more than 55,000 yearly admissions. Hospital Nacional Almenara and Hospital Nacional Loayza are similar in size, both with approximately 800 beds and 2,500 yearly admissions. Hospital Casimiro Ulloa is the smallest center with only 76 beds; however, this is a Trauma and Emergency Medicine center and thus the number of ED visits and yearly admissions is much higher than would be expected for a hospital of this size. Annual ICU mortality for all ICUs was quite similar, ranging from 16.7% to 22.9%, and average annual ICU mortality is similar to that of the JHH MICU.

ICU organization and structure

The five ICUs in Peru also share several structure (Table 2) and process related factors (Table 3) in common. They are all closed ICUs with a 24-hour, in-hospital attending intensivist coverage (vs. the high-intensity, daytime coverage only model at JHH MICU) and with a variable number of critical care fellows and residents depending on the size of the teaching program. The Peruvian ICUs average a ratio of 2 beds per nurse (ranging from 1.3:1 to 3:1) and there are

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

physician assistants or nurse practitioners in the ICU as in the JHH MICU. A notable difference between the Peruvian ICUs and the JHH MICU is the absence of respiratory therapists in the former. Since there are no established ventilation protocols in use at the Peruvian ICUs and ventilator settings are based on intensivist preference. Delirium assessment is not commonly practiced by ICU nurses in Peru whereas this is standard of care at the JHH MICU. Finally, a daily goals of care checklist is inconsistently used across participating ICUs in Peru.

Another difference between the Peruvian ICUs and JHH MICU is the presence of a multi-disciplinary team during rounds (Table 3). Medical rounds the Peruvian ICUs is comprised only by physicians (attending intensivists, residents and fellows). Nurses do not round with the medical staff and instead hold their own rounds during shift change. Also, there are no pharmacists, physical therapists, social workers, nutritionists or palliative care specialists during rounds. The main communication between nursing and medical staff occurs once a day during a meeting between the attending physician and charge nurse. Finally, Peruvian ICUs do not have either electronic patient records or computerized order entry systems as does the JHH MICU.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

This study is designed to characterize patient outcomes and clinical practices in mechanically ventilated patients in five Peruvian ICUs located at four public hospitals, and to compare with patients that have a similar distribution in age, sex and severity of illness in an academic medical center in the United States and, if possible, also with patients enrolled in contemporary multi-center studies. Specific patient-centered outcomes include 90 day mortality, time on mechanical ventilation, length of ICU and hospital stay, and prevalence of ARDS. Selected aspects of clinical management include ventilator management, sedation management, use of laboratory data to drive clinical decision making among other preventive strategies commonly used in critical care. We hypothesize that significant differences exist in the management of mechanically ventilated patients in LMICs and that these differences result in an increased mortality and a longer length of stay even when adjusted for severity. We aim to identify best practices and standardized care tailored to resource-limited settings that may result in improved patient-centered outcomes.

While international comparisons can be notoriously difficult because of inherent differences in admission criteria and discharge practices across countries, we speculate that critical care performed in resource-limited settings will likely show negative effects on patient-centered outcomes. Much of these negative effects are likely driven by limitations of resources. What is not known is the degree to which these limitations affect patient-centered outcomes and which specific treatments or interventions are most responsible for these differences. Reasons for the expected disparity in patient-centered outcomes between LMIC and HIC are likely to be multifactorial.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

What is thought to constitute best practices in critical care around the world and what can be effectively translated to resource-limited settings? Several critical care societies and organizations (19-23) have assembled guidelines to help direct and standardize care of critically-ill patients. Standardization of care can be either structure (i.e., conditions under which patient care is provided) or process related (i.e., activities that constitute patient care). Structure related factors, such as availability of nurse and ancillary medical staffing, are generally more difficult to implement. For example, during implementation of this study, we found that Peru does not have respiratory therapy practitioners, and ventilator management is done by residents and attending physicians. Moreover, lack of ancillary services such as social worker and other post-acute services may have a significant impact on patient-centered outcomes such as length of stay. Process-related factors may allow for cost-effective interventions through standardization of clinical management. There is strong evidence-based support of process-based interventions such as low tidal volumes for lung protective ventilation (24, 25), restrictive blood transfusion practices (26 ,27), early-goal directed therapy (28, 29), conservative fluid management strategies (30) and standardized sedation management and weaning protocols (31, 32). However, potential challenges exist with implementation of process-related factors, such as common practices and beliefs that are institution or country specific.

Our study has some potential shortcomings. While the case-report forms implemented in this study are exhaustive, we were unable to collect information on standardized evaluation tools for delirium such CAM-ICU (33), which are not used in Peruvian ICUs. Second, given that our study extends over a period of three years, our observational study may potentially lead to changes in clinical practice (i.e., Hawthorne effect) based on the types of questions asked in our case-report forms. Third, some information will only be available in subsets of data because not

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

all patients had daily or even weekly laboratory data collected due to resource limitations at our Peruvian ICUs. Fourth, we were limited by budget to collect prospective data from only one academic medical center in the United States. Nonetheless, we will also have the opportunity to compare clinical outcomes with those in contemporary multi-center studies (34, 35). Finally, caution will be needed in applying the results to other LMICs because of differences in healthcare delivery and medical education.

CONCLUSIONS

This study represents a large initiative to establish a Network of ICUs in Peru and understand selected aspects of clinical management and patient-centered outcomes of mechanically ventilated patients. We aim to identify potential aspects of clinical care that can be improved to reduce mortality and decrease length of stay at participating ICUs. The implementation of best practices in resource-limited settings could provide important benefits to patients but also reduce costs. In general, as the economy of any country improves, a larger portion of that country's resources will be diverted towards healthcare, and thus critical care medicine will become more sophisticated. As resources allocated to ICU medicine become more available, the ICU personnel must determine the best way to employ these resources. This study aims to identify differences in treatment that account for mortality differences between the ICUs of a developing nation compared to those of the United States. If the causative agents for major differences in mortality are isolated, protocols directed at their mitigation could result in maximizing lives saved per dollar allocated.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abbreviations: Intensive care unit = ICU; Acute respiratory distress syndrome = ARDS; Chest X-ray; Low- and middle-income countries = LMIC; Medical Intensive Care Unit = MICU; HIC High income countries; Case report form = CRF; Baseline Clinical Information Form = BCI: Daily Clinical Information Form = DCI; Study Termination Form = STF; APACHE II Form = A2F; APACHE III Form = A3F; Mortality Probability Model III Form = MPM; Sequential Organ Failure Assessment Form = SOF; ARDS Follow-up Form = AFF; Sepsis Evaluation Form = SEF; Participant identification code = PID; Emergency Department = ED.

Other members of the INTENSIVOS Cohort Study: Maria Alejandra Caravedo, Jorge Cerna, Long Davalos, Aldo De Ferrari, Maria Alejandra Pereda, Nicole Mongilardi, Navid Shams, Carmen Paredes.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Funding source: This study was supported by a Pathway to Independence Award (R00HL096955) from the National Heart, Lung and Blood Institute, National Institutes of Health. The funding agency had no role in study design or conduct, or in the writing of this report.

Conflict of interests: The authors do not have any conflicts of interest to disclose.

Authors' contributions: JD and FC were equally responsible for writing of the manuscript and participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in the design and conduct of this study and assisted in writing of manuscript. WC conceived the study and had ultimate oversight over study design and conduct, and writing of manuscript

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Chalfin DB. Cost-effectiveness analysis in health care. *Hosp Cost Manag Account* 1995;7(4):1-8.
2. Wunsch H, Linde-Zwirble WT, Angus DC et al. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38(10):1947-53.
3. Moerer O, Schmid A, Hofmann M et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. *Intensive Care Med* 2002;28(10):1440-6.
4. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med 2005;33(6):1266-71.
5. Linko R, Suojaranta-Ylinen R, Karlsson S, Ruokonen E, Varpula T, Pettilä V; FINNALI study investigators: One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. *Crit Care 2010*;14(2):R60.
6. Dünser MW, Baelani I, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. *Crit Care Med* 2006;34(4):1234-42.
7. Adhijari N K, Fowler R A, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010;376(9749):1330-46.
8. Esteban A, Anzueto A, Frutos F et al; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287(3):345-55.
9. Fowler RA, Adhikari NK, Bhagwanjee S. Clinical review: critical care in the global context--disparities in burden of illness, access, and economics. *Crit Care* 2008;12(5):225.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. *Curr Opin Crit* Care 2012;18(6):700-6.

11. Cooke CR, Kahn JM, Watkins TR, Hudson LD, Rubenfeld GD. Cost-effectiveness of implementing low-tidal volume ventilation in patients with acute lung injury. *Chest* 2009;136(1):79 - 88.

12. Squires DA. Explaining high health care spending in the United States: an international comparison of supply, utilization, prices, and quality. *Issue Brief (Commonw Fund)* 2012;10:1-14.

13. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;61(12):1234-4.

14. LeGall Jr, Loirat P, Alpérovitch A. APACHE II – a severity of disease classification system. *Crit Care Med* 1986;14(8):754-5.

15. Knaus WA, Wagner DP, Draper EA et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619-36.

16. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23(10):1638-52

17. Higgins TL, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007;35(3):827-35.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286(14):1754-8.

19. Jahn N, Kaisers UX; American Thoracic Society; European Respiratory Society; European Society of Intensive Care Medicine; Society of Critical Care Medicine; Société de Réanimation de Langue Française. Targeted temperature management in critical care : current 2011 recommendations. *Anaesthesist* 2012;61(6):550-2.

20. Sinuff T, Muscedere J, Adhikari NK et al; for the KRITICAL Working Group, the Canadian Critical Care Trials Group, and the Canadian Critical Care Society: Knowledge Translation Interventions for Critically Ill Patients: A Systematic Review. *Crit Care Med* 2013 doi: 10.1097/CCM.0b013e3182982b03.

21. Reinhart K, Perner A, Sprung CL etal; European Society of Intensive Care Medicine: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012;38(3):368-83.

22. Myburgh JA, Finfer S, Bellomo R et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012;367(20):1901-11.

23. Dellinger RP, Levy MM, Rhodes A et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39(2):165-228.

24. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

25. Amato MB, Barbas CS, Medeiros DM et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347-54.

26. Parsons EC, Hough CL, Seymour CW et al; NHLBI ARDS Network. Red blood cell transfusion and outcomes in patients with acute lung injury, sepsis and shock. Crit Care 2011;15(5):R221.

27. Hébert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409-17.

28. Rivers E, Nguyen B, Havstad S et al. Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368-77.

29. Nguyen HB, Corbett SW, Steele R et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007;35(4):1105-12.

30. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP er al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564-75.

31. MacIntyre NR, Cook DJ, Ely EW Jr et al. American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001;120(6 Suppl):375S-95S.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

32. Girard TD, Kress JP, Fuchs BD et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. *Lancet* 2008; 371(9607):126-34

33. Ely EW, Margolin R, Francis J et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29(7):1370-9.

34. Ali NA, Gutteridge D, Shahul S, Checkley W, Sevransky J, Martin GS. Critical illness outcome study: an observational study of protocols and mortality in intensive care units *Open Access Journal of Clinical Trials* 2011; 3:55-65.

35. Checkley W, Brower R, Korpak A, Thompson BT; Acute Respiratory Distress Syndrome Network Investigators. Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008;177:1215-22.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 1. Flowchart of participating intensive care units.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 2. Sequence of data submission.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Hospital characteristics and utilization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
Hospital characteristics						
Annual ICU mortality (%)	19.9	20.4	22.9	18.1	16.7	19
Type of hospital	Public (ESSALUD)	Public (ESSALUD)	Public (ESSALUD)	Public (MINSA)	Public (MINSA)	Private, non for profit
Teaching hospital	Yes	Yes	Yes	Yes	Yes	Yes
Critical care training program	Yes	Yes	Yes	Yes	Yes	Yes
Rapid response team	Yes	No	No	No	No	Yes
Electronic patient record	No	No	No	No	No	Yes
Computerized order entry	No	No	No	No	No	Yes
Number of Beds						
Adult beds at hospital	950	1526	1526	800	76	854
Adult ICU beds at hospital	60	69	69	13	16	100
Adult step down beds at hospital	80	114	114	12	6	54
Pediatric ICU beds at hospital	12	9	9	10	0	80
Beds in study ICU	21	24	11	8	11	24
Utilization						
Annual ED visits	140,000	225,300	225,300	71,660	93,000	84,892
Annual hospital admissions	30,000	55,750	55,750	2,685	3,800	48,487
Annual study ICU admissions	300	386	386	200	580	900

For peer review only

Table 2. Intensive care unit staffing and organization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU staffing						
Intensivist in ICU	Yes	Yes	Yes	Yes	Yes	Yes
24/7 intensivist	Yes	Yes	Yes	Yes	Yes	No
Leapfrog compliant?	Yes	Yes	Yes	Yes	Yes	Yes
Number of ICU fellows	4	3	2	3	1	2
24/7 ICU fellow	2	0	0	1	0	No
Number of ICU residents	4	1	1	6	1	10
Number of RTs in ICU	0	0	0	0	0	2
Number of ICU nurses	7	11	5	6	4	11
Ratio of beds to nurses	3:1	2.2:1	2.2:1	1.3:1	2.8:1	1.8:1
Number of PAs	0	0	0	0	0	3
Number of NPs	0	0	0	0	0	4
Charge nurse provides patient care?	Yes	Yes	Yes	Yes	Yes	Yes
ICU Organization						
Closed unit	Yes	Yes	Yes	Yes	Yes	Yes

For peer review only

	Has medical director	Yes	Yes	Yes	Yes	Yes	Yes
	Has nurse manager	Yes	Yes	Yes	Yes	Yes	Yes
	Has clinical nurse specialist	No	No	No	No	No	Yes
	CRRT in ICU	Yes	No	No	No	No	Yes

For peer review only

Table 3. Process related factors in participating ICUs.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU rounding practices						
Pharmacist on rounds	No	No	No	No	No	Yes
Respiratory therapist on rounds	No	No	No	No	No	Yes
Physical therapist on rounds	No	No	No	No	No	Yes
Social worker on rounds	No	No	No	No	No	No
Nutritionist on rounds	No	No	No	No	No	No
Palliative care on rounds	No	No	No	No	No	No
Delirium assessment by nursing	No	No	No	No	No	Yes
Daily goals of care checklist	Yes	No	No	No	Yes	Yes
Daily meeting between physician and charge nurse	Yes	Yes	Yes	Yes	Yes	Yes
Median number of protocols	0	0	0	0	0	19

For peer review only

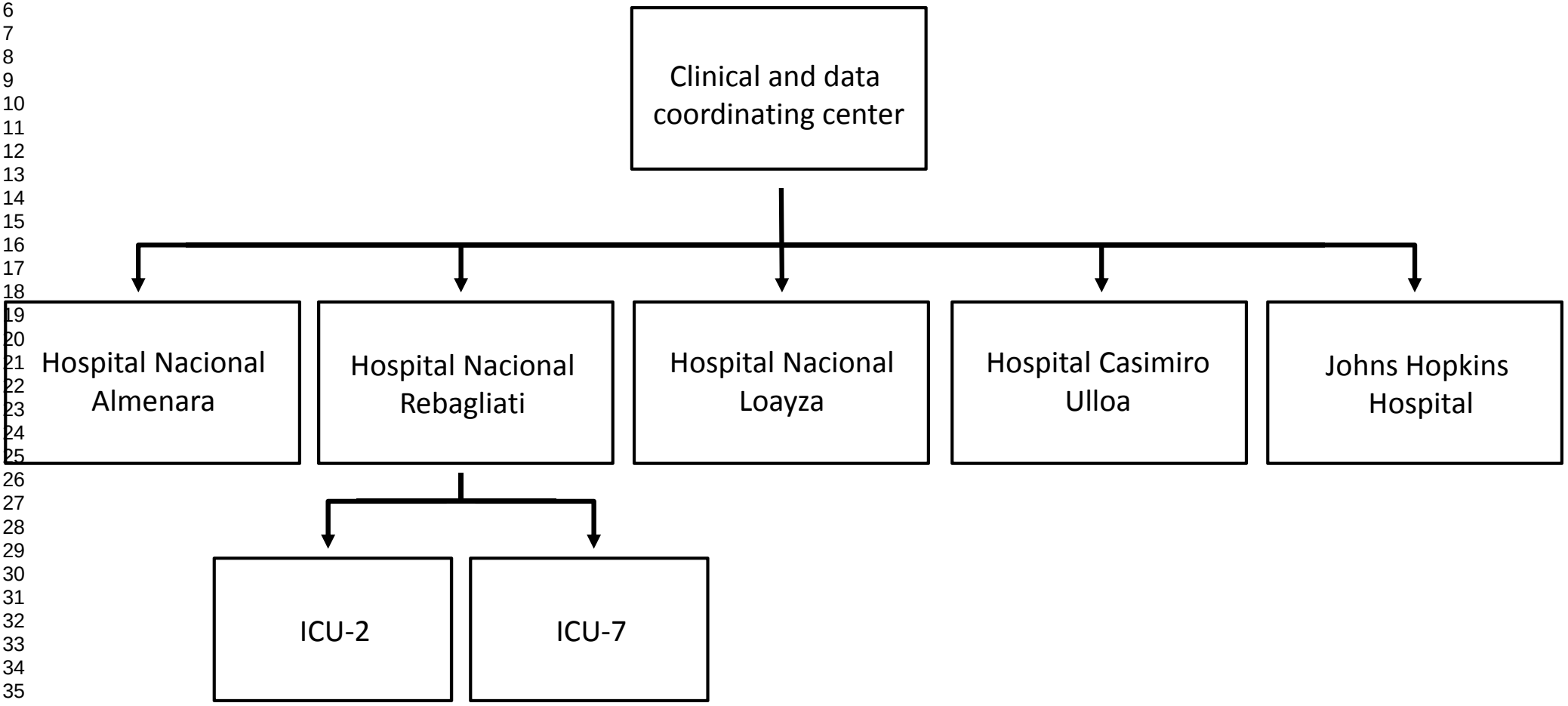
Clinical and data coordinating center
Hospital Nacional Almenara
Hospital Nacional Rebagliati
Hospital Nacional Loayza
Hospital Casimiro Ulloa
Johns Hopkins Hospital
ICU-2
ICU-7

Figure 1.

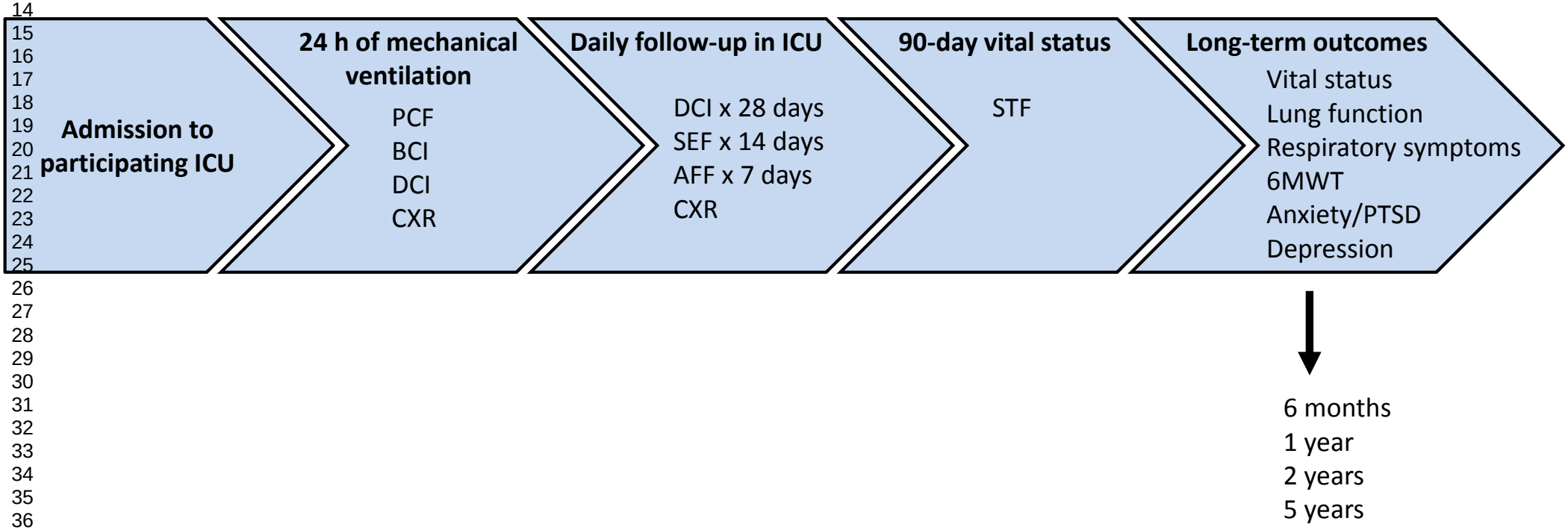
Admission to participating ICU
24 h of mechanical ventilation
PCF
BCI
DCI
CXR
Daily follow-up in ICU
DCI x 28 days
SEF x 14 days
AFF x 7 days
CXR
90-day vital status
STF
Long-term outcomes
Vital status
Lung function
Respiratory symptoms
6MWT
Anxiety/PTSD
Depression
6 months
1 year
2 years
5 years

Figure 2.

BMJ Open

Establishment of a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru: Protocol and organizational characteristics of participating centers

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005803.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Nov-2014
Complete List of Authors:	Checkley, William; Johns Hopkins University, Division of Pulmonary and Critical Care Denney, Joshua; Johns Hopkins University, Division of Pulmonary and Critical Care Capanni, Francesca; Johns Hopkins University, Division of Pulmonary and Critical Care Herrera, Phabiola; Johns Hopkins University, Division of Parasitic Diseases Dulanto, Augusto; Johns Hopkins University, Division of Pulmonary and Critical Care Roldan, Rollin; ESSALUD, Servicio de Cuidados Intensivos Paz, Enrique; ESSALUD, Servicio de Cuidados Intensivos Jaymez, Amador; MINSA, Servicio de Cuidados Intensivos Chirinos, Eduardo; MINSA, Servicio de Cuidados Intensivos Portugal, Jose; ESSALUD, Servicio de Cuidados Intensivos Quispe, Rocio; ESSALUD, Servicio de Cuidados Intensivos Brower, Roy; Johns Hopkins University, Division of Pulmonary and Critical Care
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY, Thoracic medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

Establishment of a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru: Protocol and organizational characteristics of participating centers

Joshua A Denney (1), Francesca Capanni (1), Phabiola Herrera (1), Augusto Dulanto (2), Rollin Roldan (3), Enrique Paz (4), Amador A Jaymez (5), Eduardo E Chirinos (6), Jose Portugal (3), Rocio Quispe (3), Roy G Brower (1), William Checkley (1, 7); INTENSIVOS Cohort Study.

1. Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, USA.
2. Biomedical Research Unit, Asociacion Benefica PRISMA, Lima, Peru.
3. Servicio De Cuidados Intensivos, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.
4. Servicio De Cuidados Intensivos, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru.
5. Servicio De Cuidados Intensivos, Hospital Nacional Arzobispo Loayza, Lima, Peru.
6. Servicio De Cuidados Intensivos, Hospital De Emergencias José Casimiro Ulloa, Lima, Peru.
7. Program in Global Disease Epidemiology and Control, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA.

For peer review only

Corresponding author:

William Checkley MD, PhD

Division of Pulmonary and Critical Care

School of Medicine

Johns Hopkins University

1800 Orleans Ave Suite 9121

Baltimore, MD 21205

Email: wcheckl1@jhmi.edu

Telephone: 443-287-8741

Other members of the INTENSIVOS Cohort Study: Maria Alejandra Caravedo (AB PRISMA), Jorge Cerna (Hospital Rebagliati), Long Davalos (AB PRISMA), Aldo De Ferrari (Johns Hopkins University), Maria Alejandra Pereda (AB PRISMA), Nicole Mongilardi (Johns Hopkins University), Navid Shams (Johns Hopkins University), Carmen Paredes (AB PRISMA).

Funding source: This study was supported by a Pathway to Independence Award (R00HL096955) from the National Heart, Lung and Blood Institute, National Institutes of Health. The funding agency had no role in study design or conduct, or in the writing of this report.

Conflict of interests: The authors do not have any conflicts of interest to disclose.

For peer review only

Contributorship: JD and FC were equally responsible for writing of the manuscript and participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in the design and conduct of this study and assisted in writing of manuscript. WC conceived the study and had ultimate oversight its design and conduct, and writing of this manuscript.

For peer review only

ABSTRACT

Introduction: Mechanical ventilation is a cornerstone in the management of critically ill patients worldwide; however, less is known about the clinical management of mechanically ventilated patients in low- and middle-income countries (LMICs) where limitations of resources including equipment, staff and access to medical information may play an important role in defining patient-centered outcomes. Here we present the design a prospective, longitudinal study of mechanically ventilated patients in Peru that aims to describe a large cohort of mechanically ventilated patients to identify practices that, if modified, could result in improved patient-centered outcomes and lower costs.

Methods and Analysis: Five Peruvian ICUs and the Medical ICU at the Johns Hopkins Hospital were selected for this study. Eligible patients were those who underwent at least 24 hours of invasive mechanical ventilation within the first 48 hours of admission into the ICU. Information on ventilator settings, clinical management and treatment were collected daily for up to 28 days or until the patient was discharged from the unit. Vital status was assessed at 90 days post enrollment. A subset of participants who survived until hospital discharge were asked to participate in an ancillary study to assess vital status, and physical and mental health at 6 months, 12 months, 24 months and 60 months after hospitalization, Primary outcomes include 90-day mortality, time on mechanical ventilation, hospital and ICU length of stays, and prevalence of ARDS. In subsequent analyses, we aim to identify interventions and standardized care strategies that can be tailored to resource-limited settings and that result in improved patient-centered outcomes and lower costs.

For peer review only

Ethics and Dissemination: We obtained ethics approval at each of the four participating hospitals in Lima, Peru and at the Johns Hopkins School of Medicine, Baltimore, USA. Results will be disseminated as several separate publications in different international journals.

Keywords: ICU, Critical Care, Outcomes, Protocols, ICU organization

For peer review only

INTRODUCTION

Mechanical ventilation has become a mainstay of therapy in the care of critically-ill patients. Intensive care unit (ICU) practices, mechanical ventilation strategies and their societal costs in high-income countries (HIC) are well documented. For example, in Germany, Chalfin (1) calculated that ICU care comprised 20% of hospital costs. In the United States, Wunsch *et al.* projected that 3% of inpatient hospitalizations required mechanical ventilation in 2005, comprising 30% of all ICU admissions and accounting for a disproportionate 12% of all hospital costs (2). Factors contributing to a higher cost of an individual ICU stay include sepsis and initiation of mechanical ventilation. (3, 4) Despite the higher cost and quality of care that an ICU setting implies, mortality remains high. In the United States, studies show that approximately 30% of all patients requiring mechanical ventilation die before ICU discharge (2). A Finnish study estimated a one-year mortality rate of 35% for patients receiving more than 6 hours of continuous mechanical ventilation (5).

In resource-limited settings, however, less is known about clinical practices and mechanical ventilation strategies used in critically-ill patients (6). Moreover, the burden of critical illness in low- and middle-income countries (LMICs), is higher than generally perceived and it is expected to increase with an aging population (6, 7). Esteban *et al.* analyzed data from 361 ICUs in 20 countries across the Americas and Europe and showed a statistically significant mortality difference between the United States, European, and Latin American ICUs for all patients receiving mechanical ventilation within a one month period, i.e., 27% vs. 31% vs. 34%, respectively (8). Their analysis demonstrates that disparities in mortality rates in ICUs of varying geographical and socioeconomic status exist, but did not address what factors may be

For peer review only

contributing to these differences (8). Furthermore, the results from Latin America aggregate data from countries of varying income, which may mask higher mortality rates in poorer settings.

ICUs with fewer resources and greater economic limitations may have essential differences in delivery of critical care with resulting variations in patient-centered outcomes. These disparities and their effect are not well understood (6, 9, 10). Implementation of proven ICU protocols can reduce both mortality and costs (9). Process-driven interventions, such as standardized protocols of care, could potentially play a large role in minimizing costs while improving patient outcomes which could be especially advantageous in resource-limited settings (6, 9). Our study focuses on critically-ill patients receiving mechanical ventilation in LMICs with significant resource limitations. Our goal is to better understand best practices in resource-limited settings and identify potential changes that could drive significant improvements in outcomes.

We present the design of a prospective, longitudinal cohort of mechanically ventilated patients in Lima, Peru, in five ICUs of public hospitals in Peru and one ICU in an academic medical center in the United States. The study was designed to characterize etiologies and treatment decisions most frequently seen in mechanically ventilated patients, and their relation patient-centered outcomes such as 90-day mortality, time on mechanical ventilation and ICU and hospital length of stay. With this information, we aim to identify best practices and standardized care strategies that can be tailored to resource-limited settings and applied in the future in these ICUs to improve patient-centered outcomes and lower costs.

For peer review only

METHODS

Study Objectives

We sought to characterize 90-day mortality, time spent on mechanical ventilation, ICU and hospital length of stay, mechanical ventilation strategies and selected aspects of clinical management of critically-ill patients requiring at least 24 hours of invasive mechanical ventilation in five ICUs in Lima, Peru and in one ICU in the United States (Figure 1). We further sought to characterize the proportion of patients admitted to the ICU with acute respiratory distress syndrome (ARDS); proportion of patients who developed ARDS while in the ICU; and, vital status, physical and mental health at 6, 12, 24 and 60 months after hospitalization in a subset of participants.

Outcomes

Primary outcomes for this study are 90-day mortality, time on mechanical ventilation, ICU and hospital lengths of stay, and prevalence of ARDS. Additional outcomes include vital status at 6, 12, 24 and 60 months for survivors to hospital discharge among participants in Peruvian ICUs. A subset of participants will be asked to undergo a follow-up evaluation at 6 months after the date of ICU admission to assess long-term physical and emotional impact of their hospital stay.

Study Design

The INTENSIVOS ("critical" in Spanish) cohort is a prospective, observational study. Enrollment began in December 2010 and ended in October 2013. Vital status follow-up and evaluation of physical and mental health in a subset of survivors will continue through October 2018. This manuscript was written concurrently with the implementation of the protocol and start

For peer review only

of this study. At enrollment, we obtained demographic, chronic disease and acute physiological data for all patients meeting eligibility criteria. They were followed daily to monitor vital status, clinical and ventilator management, acute physiology and use of sedation during their ICU stay for up to 28 days in the ICU, until ICU discharge or death. Patients successfully discharged from the ICU were followed for vital status during their inpatient hospital stay. All patients were contacted at 90 days after enrollment to assess vital status. A subset of participants who survived until hospital discharge were asked to participate in an ancillary study and undergo a battery of tests to assess physical and mental health after hospitalization. We aim to include 150 participants. Long-term outcomes will include vital status at 6, 12, 24 and 60 months, lung function, six-minute walk test, handgrip strength, respiratory symptoms, presence of anxiety or post-traumatic stress disorder (PTSD) and depression. The instruments used to evaluate these outcomes include the Hospital Anxiety and Depression Scale (13), the European Quality of Life 5 Dimensions 5 Levels Classification System (14), the Pittsburg Sleep Quality Index (15), the Impact of Event Scale – Revised (16), the Telephone Interview for Cognitive Status (17), the 36-item short-form health survey (18) and the Katz and Lawton-Brody Activities of Daily Living Scale.

We obtained Institutional Review Board (IRB) approval at each of the four participating hospitals in Lima, Peru: Hospital Nacional Edgardo Rebagliati Martins, Hospital Nacional Guillermo Almenara Irigoyen, Hospital Nacional Arzobispo Loayza and Hospital de Emergencias Casimiro Ulloa. In the United States, IRB approval was obtained from the Johns Hopkins School of Medicine, Baltimore, USA. All IRBs provided a waiver of consent for this study.

For peer review only

Eligibility criteria

Eligibility criteria were: 1) age ≥18 years, 2) at least 24 hours of invasive mechanical ventilation in one of the ICUs participating in the study and 3) enrollment into the study within 48 hours of onset of mechanical ventilation.

Study Sites

The study was conducted in five ICUs at four public hospitals of the Social Security System (ESSALUD) and Ministry of Health (MINSA) in Lima, Peru; and, in the Medical Intensive Care Unit (MICU) of Johns Hopkins Hospital (Figure 2). We invited only one ICU per hospital with the exception of Hospital Rebagliati, for which we included two ICUs. Participating ICUs were selected on the basis of high case volume and willingness to participate. A four-week test period was initially carried out at each hospital in Peru to determine feasibility and monthly case volume. Of six hospitals evaluated in Peru, two were unable to meet established *a priori* requirements during the test period and were not invited to continue in the study.

Study team

Data collection and quality control was organized using a tiered approach. At each ICU, a team of 2 to 7 study nurses were responsible for paper-based data collection on a daily basis and an ICU physician (co-investigators) who supervised data collection and who was responsible for data quality, review of clinical and ventilator data and interpretation of chest X-rays (CXR). In addition, a team of two study physician coordinators from the Clinical and Data Coordinating Center (DCC) oversaw the day-to-day operations of the study and act as liaisons between the principal investigator and co-investigators. The DCC is composed of team members located both

For peer review only

in Peru and the United States. Study physician coordinators visited each ICU on average two to three times a week to verify data accuracy and fidelity along with co-investigators and study nurses, perform range checks and obtain an electronic copy of CXRs. Incomplete or incorrectly entered case report forms (CRFs) were returned to study nurses for revision of missing or flagged data. Data forms were collected from all ICUs on a weekly basis and transferred to the DCC office in Peru for double data entry to a centralized database. The DCC data manager also conducted a careful review, and incomplete or incorrectly entered CRFs were returned to the study physician coordinators, who review missed or flagged data with co-investigators and study nurses. Finally, a DCC nurse was responsible for follow-up telephone calls to assess 90-day vital status and invited participants to join the long-term outcomes ancillary study among survivors.

Case Report Forms

CRFs were modeled after forms used by ARDS Network trials with additional fields added to capture the Charlson comorbidity index (19), APACHE II (20), APACHE III (21), MODS (22), Mortality Probability Model III (23) and SOFA scores (24). The CRFs were designed to capture demographics and chronic health information at baseline and daily information on acute physiology, selected aspects of clinical management, mechanical ventilation and weaning practices, and sedation management. Forms were originally written in English, translated into Spanish and then back-translated into English to confirm accuracy of translation.

Prior to study start, the study team underwent an in-person training session on how to accurately record data in paper-based CRFs. In-person training sessions were repeated approximately every six months during the first two years. All study team members were provided with a manual of operations with instructions on how to accurately fill the forms. These

For peer review only

forms were completed in black or blue ink, reviewed by co-investigators and study physician coordinators and then transferred to the DCC where they were double-data entered into a centralized database. The CRFs were: a Patient Contact Form (PCF), Baseline Clinical Information Form (BCI), Daily Clinical Information Form (DCI), and a Study Termination Form (STF). Paper-based worksheets to calculate ICU severity scores such as APACHE II (A2F), APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA (SOF) were also provided to the study team. Two additional forms were added later on and are available in a subset of study participants: ARDS Follow-up Form (AFF), in which study team members record additional ventilator parameters during the first 7 days after onset in patients that met criteria for ARDS; and, Sepsis Evaluation Form (SEF), which recorded additional clinical parameters associated with sepsis during the first 14 days after enrollment.

The PCF included patient information such as name, date of birth, address and telephone contact information for determination of follow-up of vital status after hospital discharge. This is the only form that contained protected patient information linked to a corresponding unique participant identification code (PID) in the study. The PCFs were stored in locked cabinets, and the electronic database was only available to the DCC data manager and to the nurse in charge of follow-up telephone calls. To complete subsequent forms pertaining to a specific patient, the PID was transcribed exactly as it appeared on the PCF. PIDs were checked daily by ICU team members for verification of their accuracy. The PCFs for individual patients served as the only link between medical information and patient identifying information, and will be destroyed upon completion of the study.

The BCI was completed upon patient admission to the ICU. If a patient was readmitted to the ICU, a new BCI was filled. The BCI collected information in the first 24 hours of mechanical

For peer review only

ventilation The BCI also recorded height, chronic health information and acute physiology data. Height wad measured following a standardized approach while in supine position. The BCI also had screening criteria for ARDS modeled after that used by the ARDS Network to assess whether or not a patient had ARDS upon enrollment.

The DCI was collected daily, considering day 0 as the first 24 hours of mechanical ventilation. It consisted of daily laboratory tests (complete blood count, comprehensive metabolic panel, arterial blood gas results), selected aspects of clinical management (fluid management, delirium management, prevention of ventilator-associated pneumonia, gastrointestinal ulcers and venous thromboembolism, lung protective ventilation, transfusion practices, use of central lines, arterial catheter and pulmonary artery catheters), mechanical ventilation management (mode of ventilation, tidal volume, airways pressures, oxygenation and PEEP), and use of medications such as vasopressors, medications for prophylaxis for prevention of gastrointestinal ulcers and venous thromboembolism, opioids, benzodiazepines, sedatives, neuromuscular blockers, anti-psychotics and antibiotics. DCIs were completed daily for the first 28 days or until patients died or were discharged from the ICU. Data for the DCI was captured over a defined 24-hour period of time. To ensure that data was captured only once it was necessary to create an arbitrary 24-hour period (i.e., a study day). A study day was defined as the 24 hours prior to 8 A.M. on the day of data collection. Participating hospitals were instructed to enter data for each DCI using values obtained as close as possible to 8 A.M.

The STF was used to record 90-day mortality and other ICU milestones such as time on mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-hospital deaths were also recorded. Patients were followed throughout their hospital stay after ICU discharge to determine date of hospital discharge or death. Vital status was assessed on the

For peer review only

STF at 15, 30, 45, 60 and 90 days after initiation of mechanical ventilation. After hospital discharge, vital status was obtained via a telephone call at 90 days and at subsequent dates as part of the long-term outcomes sub-study.

Although participating ICUs in Peru are in the process of acquiring the necessary infrastructure for electronic medical records, none currently have it in place. Thus, data collectors manually record all data in paper-based forms. Although the CRFs have a section to record CXR findings, digital copies of all corresponding CXR were also obtained and stored.

Sample size

Enrollment spanned a period of three years. We aimed to enroll at least 300 patients at each participating ICU for a total of 1800 participants across all six ICUs.

Characteristics of participating ICUs

The five Peruvian ICUs that took part in this study were hosted in four public Peruvian hospitals of varying size and sources of funding, and thus there are some differences between the number of beds and influx of patients between units (Table 1). Hospital Rebagliati, site of two participating ICUs, is the largest center with over 1,500 beds and more than 55,000 yearly admissions. Hospital Nacional Almenara and Hospital Nacional Loayza are similar in size, both with approximately 800 beds and 2,500 yearly admissions. Hospital Casimiro Ulloa is the smallest center with only 76 beds; however, this is a Trauma and Emergency Medicine center and thus the number of ED visits and yearly admissions is much higher than would be expected for a hospital of this size. Reported annual ICU mortality for all ICUs was quite similar, ranging from 16.7% to 22.9%, and average annual ICU mortality is similar to that of the JHH MICU.

For peer review only

ICU organization and structure

The five ICUs in Peru also share several structure (Table 2) and process related factors (Table 3) in common. They are all closed ICUs with a 24-hour, in-hospital attending intensivist coverage (vs. the high-intensity, daytime coverage only model at JHH MICU) and with a variable number of critical care fellows and residents depending on the size of the teaching program. The Peruvian ICUs average a ratio of 2 beds per nurse (ranging from 1.3:1 to 3:1) and there are physician assistants or nurse practitioners in the ICU as in the JHH MICU. A notable difference between the Peruvian ICUs and the JHH MICU is the absence of respiratory therapists in the former. Since there are no established ventilation protocols in use at the Peruvian ICUs, ventilator settings are based on intensivist preference. Delirium assessment is not commonly practiced by ICU nurses in Peru whereas this is standard of care at the JHH MICU. Finally, a daily goals of care checklist is inconsistently used across participating ICUs in Peru.

Another difference between the Peruvian ICUs and JHH MICU is the presence of a multi-disciplinary team during rounds (Table 3). Medical rounds the Peruvian ICUs were comprised only by physicians (attending intensivists, residents and fellows). Nurses do not round with the medical staff and instead hold their own rounds during shift change. Also, there are no pharmacists, physical therapists, social workers, nutritionists or palliative care specialists during rounds. The main communication between nursing and medical staff occurs once a day during a meeting between the attending physician and charge nurse. Finally, Peruvian ICUs do not have either electronic patient records or computerized order entry systems as does the JHH MICU.

For peer review only

DISCUSSION

This study is designed to characterize patient outcomes and clinical practices in mechanically ventilated patients in five Peruvian ICUs located at four public hospitals, and to compare with patients that have a similar distribution in age, sex and severity of illness in an academic medical center in the United States and, if possible, also with patients enrolled in contemporary multi-center studies. Specific patient-centered outcomes include 90-day mortality, time on mechanical ventilation, length of ICU and hospital stay, and prevalence of ARDS. Selected aspects of clinical management include ventilator management, sedation management, use of laboratory data to drive clinical decision making among other preventive strategies commonly used in critical care. We hypothesize that significant differences exist in the management of mechanically ventilated patients in LMICs and that these differences result in an increased mortality and a longer length of stay even when adjusted for severity. We aim to identify best practices and standardized care tailored to resource-limited settings that may result in improved patient-centered outcomes.

While international comparisons can be notoriously difficult because of inherent differences in admission criteria and discharge practices across countries, we speculate that critical care performed in resource-limited settings will likely show negative effects on patient-centered outcomes. Much of these negative effects are likely driven by limitations of resources. What is not known is the degree to which these limitations affect patient-centered outcomes and which specific treatments or interventions are most responsible for these differences. Reasons for the expected disparity in patient-centered outcomes between LMIC and HIC are likely to be multifactorial.

For peer review only

What is thought to constitute best practices in critical care around the world and what can be effectively translated to resource-limited settings? Several critical care societies and organizations (25-29) have assembled guidelines to help direct and standardize care of critically-ill patients. Standardization of care can be either structure (i.e., conditions under which patient care is provided) or process related (i.e., activities that constitute patient care). Structure related factors, such as availability of nurse and ancillary medical staffing, are generally more difficult to implement. For example, Peru does not have respiratory therapy practitioners, and ventilator management is done by residents and attending physicians. Moreover, lack of ancillary services such as social worker and other post-acute services may have a significant impact on patient-centered outcomes such as length of stay. Process-related factors may allow for cost-effective interventions through standardization of clinical management. There is strong evidence-based support of process-based interventions such as low tidal volumes for lung protective ventilation (30, 31), restrictive blood transfusion practices (32 ,33), early-goal directed therapy (34, 35), conservative fluid management strategies (36) and standardized sedation management and weaning protocols (37, 38). However, potential challenges exist with implementation of process-related factors, such as common practices and beliefs that are institution or country specific.

Our study has some potential shortcomings. While the case-report forms implemented in this study are exhaustive, we were unable to collect information on standardized evaluation tools for delirium such CAM-ICU (39), which are not used in Peruvian ICUs. Second, given that our study extends over a period of three years, our observational study may potentially lead to changes in clinical practice (i.e., Hawthorne effect) based on the types of questions that were asked in our case-report forms. Third, some information will only be available in subsets of data because not all patients had daily or even weekly laboratory data collected due to resource

For peer review only

limitations at our Peruvian ICUs. Fourth, we were limited by budget to collect prospective data from only one academic medical center in the United States. Nonetheless, we will also have the opportunity to compare clinical outcomes with those in contemporary multi-center studies (40, 41). Finally, caution will be needed in applying the results to other LMICs because of differences in healthcare delivery and medical education.

CONCLUSIONS

This study represents a large initiative to establish a network of intensive care units in Peru and understand selected aspects of clinical management and patient-centered outcomes of mechanically ventilated patients. We aim to identify potential aspects of clinical care that can be improved to reduce mortality and decrease length of stay at participating ICUs. The implementation of best practices in resource-limited settings could provide important benefits to patients but also reduce costs. In general, as the economy of any country improves, a larger portion of that country's resources will be diverted towards healthcare, and thus critical care medicine will become more sophisticated. This study aims to identify clinical practices that may best explain observed differences in patient-centered outcomes. If the causative agents for major differences in mortality are isolated, protocols directed at their mitigation could result in maximizing lives saved per dollar allocated.

For peer review only

Abbreviations: Intensive care unit = ICU; Acute respiratory distress syndrome = ARDS; Chest X-ray; Low- and middle-income countries = LMIC; Medical Intensive Care Unit = MICU; HIC High income countries; Case report form = CRF; Baseline Clinical Information Form = BCI: Daily Clinical Information Form = DCI; Study Termination Form = STF; APACHE II Form = A2F; APACHE III Form = A3F; Mortality Probability Model III Form = MPM; Sequential Organ Failure Assessment Form = SOF; ARDS Follow-up Form = AFF; Sepsis Evaluation Form = SEF; Participant identification code = PID; Emergency Department = ED.

Contributorship Statement

JD and FC were equally responsible for writing of the manuscript and participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in the design and conduct of this study and assisted in writing of manuscript. WC conceived the study and had ultimate oversight over study design and conduct, and writing of manuscript.

Competing Interests

None

FIGURE LEGENDS

Figure 1. Flowchart of participating intensive care units.

Figure 2. Sequence of data submission (PCF: Patient Contact Form; BCI: Baseline Clinical Form; DCI: Daily Clinical Form; CXR: Chest X-ray form; SEF: Sepsis Evaluation Form; AFF: ARDS follow-up form; STF: Study Termination Form; RASS: Richmond Agitation-Sedation Scale; 6MWT: 6-minute walk test; PTSD: Post-traumatic stress disorder)

For peer review only

REFERENCES

1. Chalfin DB. Cost-effectiveness analysis in health care. *Hosp Cost Manag Account* 1995;7(4):1-8.
2. Wunsch H, Linde-Zwirble WT, Angus DC et al. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38(10):1947-53.
3. Moerer O, Schmid A, Hofmann M et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. *Intensive Care Med* 2002;28(10):1440-6.
4. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med 2005;33(6):1266-71.
5. Linko R, Suojaranta-Ylinen R, Karlsson S, Ruokonen E, Varpula T, Pettilä V; FINNALI study investigators: One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. *Crit Care 2010*;14(2):R60.
6. Dünser MW, Baelani I, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. *Crit Care Med* 2006;34(4):1234-42.
7. Adhijari N K, Fowler R A, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010;376(9749):1330-46.
8. Esteban A, Anzueto A, Frutos F et al; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287(3):345-55.
9. Fowler RA, Adhikari NK, Bhagwanjee S. Clinical review: critical care in the global context--disparities in burden of illness, access, and economics. *Crit Care* 2008;12(5):225.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. *Curr Opin Crit* Care 2012;18(6):700-6.

11. Cooke CR, Kahn JM, Watkins TR, Hudson LD, Rubenfeld GD. Cost-effectiveness of implementing low-tidal volume ventilation in patients with acute lung injury. *Chest* 2009;136(1):79 - 88.

12. Squires DA. Explaining high health care spending in the United States: an international comparison of supply, utilization, prices, and quality. *Issue Brief (Commonw Fund)* 2012;10:1-14.

13. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67:361-370

14. Brook R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53-72

15. Bysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburg Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Res* 1989; 28(2),193-213

16. Weiss DS, Marmar CR. The Impact of Event Scale - Revised. In: Wilson JP, Keane TM, editors. Assessing Psychological Trauma and PTSD: A Practitioner's Handbook. New York; 1997. pp. 399–411.

17. Lopez OL, Kuller LH. Telephone interview for cognitive status. *Neuroepidemiology* 2010;34(1):63-4

18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992 Jun;30(6):473-83.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

19. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;61(12):1234-4.

20. LeGall Jr, Loirat P, Alpérovitch A. APACHE II – a severity of disease classification system. *Crit Care Med* 1986;14(8):754-5.

21. Knaus WA, Wagner DP, Draper EA et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619-36.

22. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23(10):1638-52

23. Higgins TL, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007;35(3):827-35.

24. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286(14):1754-8.

25. Jahn N, Kaisers UX; American Thoracic Society; European Respiratory Society; European Society of Intensive Care Medicine; Society of Critical Care Medicine; Société de Réanimation de Langue Française. Targeted temperature management in critical care : current 2011 recommendations. *Anaesthesist* 2012;61(6):550-2.

26. Sinuff T, Muscedere J, Adhikari NK et al; for the KRITICAL Working Group, the Canadian Critical Care Trials Group, and the Canadian Critical Care Society: Knowledge Translation

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Interventions for Critically Ill Patients: A Systematic Review. *Crit Care Med* 2013 doi: 10.1097/CCM.0b013e3182982b03.

27. Reinhart K, Perner A, Sprung CL etal; European Society of Intensive Care Medicine: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012;38(3):368-83.
28. Myburgh JA, Finfer S, Bellomo R et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012;367(20):1901-11.
29. Dellinger RP, Levy MM, Rhodes A et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39(2):165-228.
30. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-8.
31. Amato MB, Barbas CS, Medeiros DM et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347-54.
32. Parsons EC, Hough CL, Seymour CW et al; NHLBI ARDS Network. Red blood cell transfusion and outcomes in patients with acute lung injury, sepsis and shock. Crit Care 2011;15(5):R221.
33. Hébert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409-17.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

34. Rivers E, Nguyen B, Havstad S et al. Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368-77.

35. Nguyen HB, Corbett SW, Steele R et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007;35(4):1105-12.

36. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP er al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564-75.

37. MacIntyre NR, Cook DJ, Ely EW Jr et al. American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001;120(6 Suppl):375S-95S.

38. Girard TD, Kress JP, Fuchs BD et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. *Lancet* 2008; 371(9607):126-34

39. Ely EW, Margolin R, Francis J et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29(7):1370-9.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

40. Ali NA, Gutteridge D, Shahul S, Checkley W, Sevransky J, Martin GS. Critical illness outcome study: an observational study of protocols and mortality in intensive care units *Open Access Journal of Clinical Trials* 2011; 3:55-65.

41. Checkley W, Brower R, Korpak A, Thompson BT; Acute Respiratory Distress Syndrome Network Investigators. Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008;177:1215-22.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Hospital characteristics and utilization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
Hospital characteristics						
Annual ICU mortality (%)	19.9	20.4	22.9	18.1	16.7	19
Type of hospital	Public (ESSALUD)	Public (ESSALUD)	Public (ESSALUD)	Public (MINSA)	Public (MINSA)	Private, non for profit
Teaching hospital	Yes	Yes	Yes	Yes	Yes	Yes
Critical care training program	Yes	Yes	Yes	Yes	Yes	Yes
Rapid response team	Yes	No	No	No	No	Yes
Electronic patient record	No	No	No	No	No	Yes
Computerized order entry	No	No	No	No	No	Yes
Number of Beds						
Adult beds at hospital	950	1526	1526	800	76	854
Adult ICU beds at hospital	60	69	69	13	16	100
Adult step down beds at hospital	80	114	114	12	6	54
Pediatric ICU beds at hospital	12	9	9	10	0	80
Beds in study ICU	21	24	11	8	11	24
Utilization						
Annual ED visits	140,000	225,300	225,300	71,660	93,000	84,892
Annual hospital admissions	30,000	55,750	55,750	2,685	3,800	48,487
Annual study ICU admissions	300	386	386	200	580	900

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Intensive care unit staffing and organization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU staffing						
Intensivist in ICU	Yes	Yes	Yes	Yes	Yes	Yes
24/7 intensivist	Yes	Yes	Yes	Yes	Yes	No
Leapfrog compliant?	Yes	Yes	Yes	Yes	Yes	Yes
Number of ICU fellows	4	3	2	3	1	2
24/7 ICU fellow	2	0	0	1	0	No
Number of ICU residents	4	1	1	6	1	10
Number of RTs in ICU	0	0	0	0	0	2
Number of ICU nurses	7	11	5	6	4	11
Ratio of beds to nurses	3:1	2.2:1	2.2:1	1.3:1	2.8:1	1.8:1
Number of PAs	0	0	0	0	0	3
Number of NPs	0	0	0	0	0	4
Charge nurse provides patient care?	Yes	Yes	Yes	Yes	Yes	Yes
ICU Organization						
Closed unit	Yes	Yes	Yes	Yes	Yes	Yes

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Has medical director	Yes	Yes	Yes	Yes	Yes	Yes
	Has nurse manager	Yes	Yes	Yes	Yes	Yes	Yes
	Has clinical nurse specialist	No	No	No	No	No	Yes
	CRRT in ICU	Yes	No	No	No	No	Yes

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Process related factors in participating ICUs.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU rounding practices						
Pharmacist on rounds	No	No	No	No	No	Yes
Respiratory therapist on rounds	No	No	No	No	No	Yes
Physical therapist on rounds	No	No	No	No	No	Yes
Social worker on rounds	No	No	No	No	No	No
Nutritionist on rounds	No	No	No	No	No	No
Palliative care on rounds	No	No	No	No	No	No
Delirium assessment by nursing	No	No	No	No	No	Yes
Daily goals of care checklist	Yes	No	No	No	Yes	Yes
Daily meeting between physician and charge nurse	Yes	Yes	Yes	Yes	Yes	Yes
Median number of protocols	0	0	0	0	0	19

3

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Establishment of ~~"INTENSIVOS"; a~~a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru: Protocol and ~~summary of~~ ~~o~~organizational characteristics ~~of~~ of participating ~~ICU~~centers

Joshua A Denney (1), Francesca Capanni (1), Phabiola Herrera (1), Augusto Dulanto (~~1~~2), Rollin Roldan (~~3~~2), Enrique Paz (~~3~~4), Amador A Jaymez (~~4~~5), Eduardo E Chirinos (~~5~~6), Jose Portugal (~~2~~3), Rocio Quispe (~~2~~3), Roy G Brower (1), William Checkley (1, ~~7~~6); INTENSIVOS Cohort Study.

1. Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, USA.
2. Biomedical Research Unit, Asociacion Benefica PRISMA, Lima, Peru.
3. Servicio De Cuidados Intensivos, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.
4. Servicio De Cuidados Intensivos, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru.
5. Servicio De Cuidados Intensivos, Hospital Nacional Arzobispo Loayza, Lima, Peru.
6. Servicio De Cuidados Intensivos, Hospital De Emergencias José Casimiro Ulloa, Lima, Peru.
7. Program in Global Disease Epidemiology and Control, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA.

Formatted: Numbered + Level: 1 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0.25" + Indent at: 0.5"

Formatted: Spanish (Peru)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Corresponding author:

William Checkley MD, PhD

Division of Pulmonary and Critical Care

School of Medicine

Johns Hopkins University

1800 Orleans Ave Suite 9121

Baltimore, MD 21205

Email: wcheckl1@jhmi.edu

Telephone: 443-287-8741

Other members of the INTENSIVOS Cohort Study: Maria Alejandra Caravedo (AB PRISMA), Jorge Cerna (Hospital Rebagliati), Long Davalos (AB PRISMA), Aldo De Ferrari (Johns Hopkins University), Maria Alejandra Pereda (AB PRISMA), Nicole Mongilardi (Johns Hopkins University), Navid Shams (Johns Hopkins University), Carmen Paredes (AB PRISMA). ~~All affiliated with the Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, USA.~~

Funding source: This study was supported by a Pathway to Independence Award (R00HL096955) from the National Heart, Lung and Blood Institute, National Institutes of Health. The funding agency had no role in study design or conduct, or in the writing of this report.

Formatted: English (U.S.)

Formatted: English (U.S.)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Conflict of interests: The authors do not have any conflicts of interest to disclose.

~~**Authors' contributions**~~**Contributorship:** JD and FC were equally responsible for writing of the manuscript and participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in the design and conduct of this study and assisted in writing of manuscript. WC conceived the study and had ultimate oversight ~~over~~ its ~~study~~ design and conduct, and writing of this manuscript.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ABSTRACT

Introduction: Mechanical ventilation is a cornerstone in the management of critically ill patients worldwide; however, less is known about the clinical management of mechanically ventilated patients in low- and middle-income countries (LMICs) where limitations of resources including equipment, staff and access to medical information may play an important role in defining patient-centered outcomes. ~~The purpose of this article is to~~ Here we present the design ~~of~~ ~~INTENSIVOS, a~~a prospective, longitudinal study of mechanically ventilated patients in Peru that aims to describe a large cohort of mechanically ventilated patients ~~in order~~ to identify practices that, if modified, ~~can~~ could result in improved patient-centered outcomes and lower costs.

Methods and Analysis: Five Peruvian ICUs and the ~~MICU~~ Medical ICU at the Johns Hopkins Hospital were selected for this study. Eli~~e~~gible patients were ~~were are~~ those who underwent at least 24 hours of invasive mechanical ventilation within the first 48 hours of admission into the ICU. Information on ventilator settings, clinical management and treatment ~~will be~~ were collected daily for up to 28 days or until the patient ~~is~~ was discharged from the unit. Vital status ~~will be~~ was assessed at 90 days post enrollment. A subset of participants who survive~~rs~~ed until hospital discharge were asked to participate in an ancillary study to assess vital status, and physical and mental health at 6 months, 12 months, 24 months and 60 months after hospitalization. Primary outcomes include 90-day mortality, time on mechanical ventilation, hospital and ICU length of stays, and prevalence of ARDS. In subsequent analyses, we aim to identify interventions and standardized care strategies that can be tailored to resource-limited settings and that ~~will r~~result in improved patient-centered outcomes and lower costs.

Formatted: Font: Not Bold, Font color: Black, Pattern: Clear

Formatted: Font: Not Bold, Font color: Black, Pattern: Clear

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ethics and Dissemination: We obtained ethics approval at each of the four participating hospitals in Lima, Peru and at the Johns Hopkins School of Medicine, Baltimore, USA. Results will be disseminated as several separate publications in different international ~~magazines~~ journals.

Keywords: ICU, Critical Care, Outcomes, Protocols, ICU organization

Formatted: Font: Font color: Black, Pattern: Clear

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Mechanical ventilation has become a mainstay of therapy in the care of critically-ill patients. Intensive care unit (ICU) practices, mechanical ventilation strategies and their societal costs in high-income countries (HIC) are well documented. For example, in Germany, Chalfin (1) calculated that ICU care comprised 20% of hospital costs. In the United States, Wunsch *et al.* projected that 3% of inpatient hospitalizations required mechanical ventilation in 2005, comprising 30% of all ICU admissions and accounting for a disproportionate 12% of all hospital costs (2). Factors contributing to a higher cost of an individual ICU stay include sepsis and initiation of mechanical ventilation. (3, 4) Despite the higher cost and quality of care that an ICU setting implies, mortality remains high. In the United States, studies show that approximately 30% of all patients requiring mechanical ventilation die before ICU discharge (2). A Finnish study estimated a one-year mortality rate of 35% for patients receiving more than 6 hours of continuous mechanical ventilation (5).

In resource-limited settings, however, less is known about clinical practices and mechanical ventilation strategies used in critically-ill patients (6). Moreover, the burden of critical illness in low- and middle-income countries (LMICs), is higher than generally perceived ~~in low- and middle-income countries (LMICs),~~ and it is expected to increase with an aging population (6, 7). Esteban *et al.* analyzed data from 361 ICUs in 20 countries across the Americas and Europe and showed a statistically significant mortality difference between the United States, European, and Latin American ICUs for all patients receiving mechanical ventilation within a one month period, i.e., 27% vs. 31% vs. 34%, respectively (8). Their analysis demonstrates that disparities in mortality rates in ICUs of varying geographical and socioeconomic status exist, but did not address what factors may be contributing to these

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

differences (8). Furthermore, the results from Latin America aggregate data from countries of varying ~~wealth~~income, which may mask higher mortality rates in poorer settings.

ICUs with fewer resources and greater economic limitations may have essential differences in delivery of critical care with resulting variations in patient-centered outcomes. These disparities and their effect are not well understood (6, 9, 10). Implementation of proven ICU protocols can reduce both mortality and costs (9). Process-driven interventions, such as standardized protocols of care, could potentially play a large role in minimizing costs while improving patient outcomes which could be especially advantageous in resource-limited settings (6, 9). Our study focuses on critically-ill patients receiving mechanical ventilation in LMICs with significant resource limitations. Our goal is to better understand best practices in resource-limited settings~~ (and identify potential changes that could drive significant improvements in outcomes)~~ and identify potential changes that could drive significant improvements in outcomes.

~~The purpose of this article is to~~ We present the design of ~~INTENSIVOS, a~~a prospective, longitudinal cohort of mechanically ventilated patients in Lima, Peru~~. [In 2009, Peru spent 5% of its gross domestic product on healthcare versus 16% in the United States and a median of 10% across European countries (12). The role of intensive care and mechanical ventilation will become increasingly important as Peru develops and its population ages.] (I think this should be mentioned earlier, not here)~~ ~~In this study, we~~ , ~~i~~will ~~characterize clinical and ventilator management of patients requiring a minimum of 24 hours of mechanical ventilation i~~n five ICUs ~~in~~ of public hospitals in Peru and one ICU in an academic medical center in the United States. ~~We hypothesize that measurable differences in patient-centered metrics such as mortality and length of~~ hospital and ICU ~~stay exist between the ICUs in LMICs and the United States.~~ ~~We will enroll patients that receive ICU care within a 48-hour window of~~

Formatted: Font: Not Bold, No underline, Font color: Black, Pattern: Clear

Formatted: Font: Not Bold, No underline, Font color: Black, Pattern: Clear

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~starting mechanical ventilation and follow them during their stay, recording prospective demographic information, daily laboratory results, ventilator settings and clinical management decisions.(already in earlier paragraphs)~~ The study ~~is~~ was designed to ~~identify~~ characterize ~~etiologies and treatment decisions~~ etiologies and treatment decisions most frequently seen in mechanically ventilated patients, ~~and compare these~~ and their relation patient-centered outcomes such as~~with~~ 90-day mortality, time on mechanical ventilation and ICU and hospital length of stay. ~~parameters.~~ With this information, ~~the ultimate goal of the study is to~~ we aim to identify best practices and standardized care strategies that can be tailored to resource-limited settings and applied in the future in these ICUs ~~in order~~ to improve patient-centered outcomes and lower costs.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS

Study Objectives

We ~~seek~~ sought to characterize 90-day mortality, time spent on mechanical ventilation, ICU and hospital length of stay, mechanical ventilation strategies and selected aspects of clinical management of critically-ill patients requiring at least 24 hours of invasive mechanical ventilation in five ICUs in Lima, Peru and in one ICU in the United States (Figure 1). We further ~~seek~~ sought to characterize the proportion of patients admitted to the ICU with acute respiratory distress syndrome (ARDS) ~~and the~~ ; proportion of patients who ~~will d~~developed ARDS while in the ICU; and, ~~-~~ vital status, physical and mental health at 6, 12, 24 and 60 months after hospitalization in a subset of participants.

~~Finally~~~~Also, we will compare the mortality rates with severity-matched patients in concurrent cohorts of ICU patients in the United States we will utilize ICU prognostic scores to stratify patients by severity of illness and compare mortality rates of critically ill patients with those of similar illness severity in concurrent cohorts of ICU patients in the United States, including the one collected in this study and in publicly available datasets.~~

Outcomes

Primary outcomes for this study ~~will be~~ are 90-day mortality, time on mechanical ventilation, ICU and hospital length~~s~~ of stay~~s~~, and prevalence of ARDS.

Additional outcomes include vital status at 6, 12, 24 and 60 months for survivors ~~in the group of patients in~~ to hospital discharge among participants in Peruvian ICUs. ~~A comparison of factors associated to 90-day mortality between the Peruvian and American ICUs will be performed. This will allow us to identify differences in patient care that may be modified in Peruvian ICUs in~~

Formatted: Font: Bold, Font color: Black, Pattern: Clear

Formatted: Font: Bold

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

order to improve patient based outcomes. Finally, aA subset of patients participants will be asked to undergo a medical examination a follow-up evaluation at 6 months after the date of ICU admission in order tto assess long-term physical and emotional impact of the their hospital stay.

Study Design

This The INTENSIVOS ("critical" in Spanish) cohort is a prospective, observational, longitudinal study conducted between . Enrollment began in December 2010 and ended in October 2013. Vital status follow-up and evaluation of physical and mental health in a subset of survivors will continue through October 2018. At the time when tThis manuscript was written all sections of the study are concurrently with the implemented and runningation of the protocol and conduct of start of this study. At enrollment, we will obtaineded demographics, chronic disease and acute physiological data for all patients meeting eligibility criteria. They will be We then were followed patients daily to monitor vital status, clinical and ventilator management, acute physiology and use of sedation during their ICU stay for up to 28 days in the ICU, until ICU discharge or death. Patients who arewere ssuccessfully discharged from the ICU will beere were followed for vital status during their inpatient hospital stay. All patients will beere were contacted at 90 days after enrollment to assess vital status. A subset of participants who All sSurvivors in Peru only will be contacted by telephone again at 6, 12, 24 and 60 months (long-term outcomes) after enrollment . The telephone call will consist of a simple interview answered by the patient (ideally) or a family member in order to assess vital status and record date of demise if applicableinto the study to assess for vital status.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~Data collected during the ICU stay will be analyzed with respect to its effect on 90-day mortality, and data from Peruvian patients will be compared to that of patients in an American ICU. This will allow us to identify differences in patient care that may be modified in Peruvian ICUs in order to improve patient-related outcomes.~~

~~Patients~~ survi~~vorsed~~ until ~~who are discharged from one of the hospitals owned by Social Security will be~~ hospital discharge were asked to participate in an ancillary study and undergo a battery of tests ~~in order~~ to assess physical and mental health after ~~the~~ hospitalization. ~~We will be using the facilities at one of the Social Security hospitals for this evaluation, and thus, it will only be available for Social Security patients.~~ We aim to include ~~150 – 200~~ 150 ~~patients~~ participants~~in this ancillary study~~. ~~The l~~Long-term outcomes will ~~will we will evaluate with this follow up~~ ~~are~~include~~:~~ vital status at 6, 12, 24 and 60 months, ~~vital status,~~ lung function, six-minute walk test, handgrip strength, respiratory symptoms, presence of anxiety or post-traumatic stress disorder (PTSD) and depression. The instruments ~~that will be~~ used to evaluate these outcomes ~~are:~~ include the ~~the HADS:~~ Hospital Anxiety and Depression Scale (13), the European Quality of Life 5 Dimensions 5 Levels Classification System (14), the Pittsburg Sleep Quality Index (15), the Impact of Event Scale – Revised (16), the ~~TICS:~~ Telephone Interview for Cognitive Status (17), the 36-item short-form health survey ~~(SF-36)~~ (18) and the Katz and Lawton-Brody Activities of Daily Living Scal~~e. Patients will also undergo clinical tests such as the 6-minute walk test, the handgrip strength test and pulmonary spirometry and carbon monoxide diffusion capacity (DLCO).~~c.

~~A subset of survivors will be asked to participate in an ancillary study and undergo a battery of tests at follow-up, including: questionnaires of quality of life, respiratory symptoms,~~

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

Formatted: Font: Times New Roman, Font color: Black, Pattern: Clear

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

~~anxiety, depression and post-traumatic stress disorder; and, clinical tests including a six-minute walk test, pulmonary function testing and handgrip strength.~~

We obtained Institutional Review Board (IRB) approval at each of the four participating hospitals in Lima, Peru: Hospital Nacional Edgardo Rebagliati Martins, Hospital Nacional Guillermo Almenara Irigoyen, Hospital Nacional Arzobispo Loayza and Hospital de Emergencias Casimiro Ulloa. In the United States, IRB approval was obtained from the Johns Hopkins School of Medicine, Baltimore, USA. All IRBs provided a waiver of consent for this study.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Formatted: Indent: First line: 0"

Eligibility criteria

Eligibility criteria ~~include~~were: 1) age ≥18 years, 2) at least 24 hours of invasive mechanical ventilation in one of the ICUs participating in the study and 3) enrollment into the study within 48 hours of onset of mechanical ventilation.

Study Sites

The study ~~is~~ was ~~was~~ conducted in five ICUs at four public hospitals of the Social Security System (ESSALUD) and Ministry of Health (MINSA) in Lima, Peru; and, in the Medical Intensive Care Unit (MICU) of Johns Hopkins Hospital (Figure 2). We invited only one ICU per hospital with the exception of Hospital Rebagliati, for which we included two ICUs. Participating ICUs ~~have beenwere~~ were selected on the basis of high case volume and willingness to participate. A four-week test period was initially carried out at each hospital in Peru to determine feasibility and monthly case volume. Of six hospitals ~~approached~~ evaluated in Peru, two were unable to meet established *a priori* requirements during the test period and were not invited to continue in the study.

Study team

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

We organized dData collection and quality control is was organized using a tiered approach. At each ICU, we identified a team of 2 to 7 study nurses who wereare were responsible for paper-based data collection on a daily basis and an ICU physician (co-investigators) who supervisedd data collection and who arewere was responsible for data quality, review of clinical and ventilator data and interpretation of chest X-rays (CXR). In addition, a team of two study physician coordinators from the Clinical and Data Coordinating Center (DCC) overseeawaw the day-to-day operations of the study and act as liaisons between the principal investigator and co-investigators. The DCC is composed of team members located both in Peru and the United States. Study physician coordinators visitedd each ICU on average two to three times a week to verify data accuracy and fidelity along with co-investigators and study nurses, perform range checks and obtain an electronic copy of CXRs. Incomplete or incorrectly entered case report forms (CRFs) arewere were returned to study nurses for revision of missing or flagged data. Data forms arewere were collected from all ICUs on a weekly basis and transferred to the DCC office in Peru for double data entry to a centralized database. The DCC data manager also conductsed ed a careful review, and incomplete or incorrectly entered CRFs arewere were returned to the study physician coordinators, who reviewed missed or flagged data with co-investigators and study nurses. Finally, a DCC nurse iswas was responsible for follow-up telephone calls to assess 90-day vital status after hospital discharge aand will invite invited invited participants to join the long-term outcomes ancillary study among survivors.

Case Report Forms

CRFs arewere were modeled after forms used by ARDS Network trials with additional fields added to capture the Charlson comorbidity index (193), APACHE II (2014), APACHE III

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(2115), MODS (2216), Mortality Probability Model III (2317) and SOFA scores (2418). The CRFs arewere were designed to capture demographics and chronic health information at baseline and daily information on acute physiology, selected aspects of clinical management, mechanical ventilation and weaning practices, and sedation management. Forms were originally written in English, translated into Spanish and then back-translated into English to confirm accuracy of translation.

Study team members at participating hospitals reviewed and tested Spanish CRFs during the pilot phase. During this pilot, differences in ICU practices between the United States and Peruvian ICUs became apparent and the CRFs were modified to accommodate differences. For example, resource limitations at participating ICUs in Peru limit laboratory data collection to a maximum of once per day per patient, with data frequently being collected less than once per day. Moreover, laboratory tests are usually individually ordered rather that in order sets. Likewise, CXRs are ordered less frequently than in ICUs in the United Stateus.

Prior to study start, the study team underwent an in-person training session on how to accurately record data in paper-based CRFs. In-person training sessions were repeated approximately every six months during the first two years. All study team members were provided with a manual of operations with instructions on how to accurately fill the forms. These forms were completed in black or blue ink, reviewed by co-investigators and study physician coordinators and then transferred to the DCC where they were doublye-datae data entered into a centralized database. The CRFs are werecomposed of four parts: a Patient Contact Form (PCF), Baseline Clinical Information Form (BCI), Daily Clinical Information Form (DCI), and a Study Termination Form (STF). Paper-based worksheets to calculate ICU severity scores such as APACHE II (A2F), APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(SOF) ~~have were also been~~ were also provided to the study team. Two additional forms ~~have beenwere~~ were added later on~~into the study~~ and ~~will be~~ are available in a subset of study participants: ARDS Follow-up Form (AFF), in which study team members record~~ed~~ additional ventilator parameters during the first 7 days after onset in patients that m~~e~~et criteria for ARDS; and, Sepsis Evaluation Form (SEF), which record~~sed~~sed~~ed~~ additional clinical parameters associated with sepsis during the first 14 days after enrollment.

The PCF include~~sd~~sd~~d~~ patient information such as name, date of birth, address and telephone contact information for determination of follow-up of vital status after hospital discharge. This is the only form that contain~~sed~~sed~~ed~~ protected patient information linked to a corresponding unique participant identification code (PID) in the study. The PCFs ~~are~~ were stored in locked cabinets, and the electronic database ~~is~~ was only available to the DCC data manager and to the nurse in charge of follow-up telephone calls. To complete subsequent forms pertaining to a specific patient, the PID ~~i~~wa~~was~~s transcribed exactly as it appeared on the PCF. PIDs were checked daily by ICU team members for verification of their accuracy. The PCFs for individual patients serve~~d~~ as the only link between medical information and patient identifying information, and will be destroyed upon completion of the study.

The BCI ~~iwas~~ was completed upon patient admission to the ICU. If a patient ~~iwas~~ was readmitted to the ICU, a new BCI ~~iwas~~ was filled. The BCI collected information in the first 24 hours of mechanical ventilation The BCI also record~~sed~~sed~~ed~~ height, chronic health information and acute physiology data. Height ~~iwas~~ wad measured following a standardized approach while in supine position. The BCI also ha~~sd~~sd~~d~~ screening criteria for ARDS modeled after that used by the ARDS Network to assess whether or not a patient ha~~sd~~sd~~d~~ ARDS upon enrollment.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The DCI ~~iwas~~ was collected daily, considering day 0 as the first 24 hours of mechanical ventilation. It consisted of daily laboratory tests (complete blood count, comprehensive metabolic panel, arterial blood gas results), selected aspects of clinical management (fluid management, delirium management, prevention of ventilator-associated pneumonia, gastrointestinal ulcers and venous thromboembolism, lung protective ventilation, transfusion practices, use of central lines, arterial catheter and pulmonary artery catheters) ~~(chest x-ray data, presence of thoracic tubes, use of central lines, use of dialysis use of insulin, etc)~~, mechanical ventilation management (mode of ventilation, tidal volume, airways pressures, oxygenation and PEEP) ~~(FiO2, ventilation mode, tidal volume, PEEP, etc)~~, and use of medications such as vasopressors, medications for prophylaxis for prevention of gastrointestinal ulcers and venous thromboembolism, ~~steroids~~opioids, benzodiazepines, sedatives, neuromuscular blockers, anti-psychotics and antibiotics. DCIs ~~arwere~~ were completed daily for the first 28 days or until patients d~~ie~~ied~~ied~~ or ~~w areas~~w-ere discharged from the ICU. Data for the DCI ~~iwas~~ was captured over a defined 24-hour period of time. To ensure that data ~~iwas~~ was captured only once it was necessary to create an arbitrary 24-hour period (i.e., a study day). A study day ~~iwas~~ was defined as the 24 hours prior to 8 A.M. on the day of data collection. Participating hospitals ~~will have beenbe~~ were instructed to enter data for each DCI using values obtained as close as possible to 8 A.M.

The STF ~~iwas~~ was used to record 90-day mortality and other ICU milestones such as time on mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-hospital deaths ~~arewere~~ were also recorded. Patients ~~arewere~~ were followed throughout their hospital stay after ICU discharge to determine date of hospital discharge or death. Vital status ~~iwas~~ was assessed o~~i~~n the STF at 15, 30, 45, 60 and 90 days after initiation of mechanical

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ventilation. After hospital discharge, vital status ~~iwas~~ was obtained via a telephone call at 90 days and at subsequent dates as part of the long-term outcomes sub-study.

Although participating ICUs in Peru are in the process of acquiring the necessary infrastructure for electronic medical records, none currently have it in place. Thus, data collectors manually record~~ed~~ all data in paper-based forms. Although the CRFs ha~~d~~ve a section to record CXR findings, digital copies of all corresponding CXR ~~arewere~~ were also obtained and stored.

Sample size

~~The study~~ Enrollment spanned a period of three years. We aimed to enroll at least 300 patients at each participating ICU for a total of 1800 participants across all six ICUs. ~~To detect a difference in 90-day mortality of 10% between a Peruvian ICU and the Johns Hopkins MICU with an expected baseline mortality of 30%, confidence level of 95% and power 90%, we estimated that we would need 240 participants per ICU. We chose to over-enroll by 20% to account for potential missing data.~~

Characteristics of participating ICUs

The five Peruvian ICUs that ~~takeook~~ took part in this study ~~arewere~~ were hosted in four public Peruvian hospitals of varying size and sources of funding, and thus there are some differences between the number of beds and influx of patients between units (Table 1). ~~The~~ Hospital Rebagliati, site of two participating ICUs, is the largest center with over 1,500 beds and more than 55,000 yearly admissions. Hospital Nacional Almenara and Hospital Nacional Loayza are similar in size, both with approximately 800 beds and 2,500 yearly admissions. Hospital Casimiro Ulloa is the smallest center with only 76 beds; however, this is a Trauma and

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Emergency Medicine center and thus the number of ED visits and yearly admissions is much higher than would be expected for a hospital of this size. Reported a~~A~~nnual ICU mortality for all ICUs was quite similar, ranging from 16.7% to 22.9%, and average annual ICU mortality is similar to that of the JHH MICU.

ICU organization and structure

The five ICUs in Peru also share several structure (Table 2) and process related factors (Table 3) in common. They are all closed ICUs with a 24-hour, in-hospital attending intensivist coverage (vs. the high-intensity, daytime coverage only model at JHH MICU) and with a variable number of critical care fellows and residents depending on the size of the teaching program. The Peruvian ICUs average a ratio of 2 beds per nurse (ranging from 1.3:1 to 3:1) and there are physician assistants or nurse practitioners in the ICU as in the JHH MICU. A notable difference between the Peruvian ICUs and the JHH MICU is the absence of respiratory therapists in the former. Since there are no established ventilation protocols in use at the Peruvian ICUs, ~~and~~ ventilator settings are based on intensivist preference. Delirium assessment is not commonly practiced by ICU nurses in Peru whereas this is standard of care at the JHH MICU. Finally, a daily goals of care checklist is inconsistently used across participating ICUs in Peru.

Another difference between the Peruvian ICUs and JHH MICU is the presence of a multi-disciplinary team during rounds (Table 3). Medical rounds the Peruvian ICUs ~~arei~~s were comprised only by physicians (attending intensivists, residents and fellows). Nurses do not round with the medical staff and instead hold their own rounds during shift change. Also, there are no pharmacists, physical therapists, social workers, nutritionists or palliative care specialists during rounds. The main communication between nursing and medical staff occurs once a day during a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

meeting between the attending physician and charge nurse. Finally, Peruvian ICUs do not have either electronic patient records or computerized order entry systems as does the JHH MICU.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

This study is designed to characterize patient outcomes and clinical practices in mechanically ventilated patients in five Peruvian ICUs located at four public hospitals, and to compare with patients that have a similar distribution in age, sex and severity of illness in an academic medical center in the United States and, if possible, also with patients enrolled in contemporary multi-center studies. Specific patient-centered outcomes include 90–day mortality, time on mechanical ventilation, length of ICU and hospital stay, and prevalence of ARDS. Selected aspects of clinical management include ventilator management, sedation management, use of laboratory data to drive clinical decision making among other preventive strategies commonly used in critical care. We hypothesize that significant differences exist in the management of mechanically ventilated patients in LMICs and that these differences result in an increased mortality and a longer length of stay even when adjusted for severity. We aim to identify best practices and standardized care tailored to resource-limited settings that may result in improved patient-centered outcomes.

While international comparisons can be notoriously difficult because of inherent differences in admission criteria and discharge practices across countries, we speculate that critical care performed in resource-limited settings will likely show negative effects on patient-centered outcomes. Much of these negative effects are likely driven by limitations of resources. What is not known is the degree to which these limitations affect patient-centered outcomes and which specific treatments or interventions are most responsible for these differences. Reasons for the expected disparity in patient-centered outcomes between LMIC and HIC are likely to be multifactorial.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

What is thought to constitute best practices in critical care around the world and what can be effectively translated to resource-limited settings? Several critical care societies and organizations (25~~19~~-29~~3~~) have assembled guidelines to help direct and standardize care of critically-ill patients. Standardization of care can be either structure (i.e., conditions under which patient care is provided) or process related (i.e., activities that constitute patient care). Structure related factors, such as availability of nurse and ancillary medical staffing, are generally more difficult to implement. For example, ~~during implementation of this study, we found that~~ Peru does not have respiratory therapy practitioners, and ventilator management is done by residents and attending physicians. Moreover, lack of ancillary services such as social worker and other post-acute services may have a significant impact on patient-centered outcomes such as length of stay. Process-related factors may allow for cost-effective interventions through standardization of clinical management. There is strong evidence-based support of process-based interventions such as low tidal volumes for lung protective ventilation (30~~24~~, 31~~25~~), restrictive blood transfusion practices (32~~26~~ ,33~~27~~), early-goal directed therapy (34~~28~~, 35~~29~~), conservative fluid management strategies (36~~0~~) and standardized sedation management and weaning protocols (37~~1~~, 38~~2~~). However, potential challenges exist with implementation of process-related factors, such as common practices and beliefs that are institution or country specific.

Our study has some potential shortcomings. While the case-report forms implemented in this study are exhaustive, we ~~are~~~~were~~ were unable to collect information on standardized evaluation tools for delirium such CAM-ICU (39~~3~~), which are not used in Peruvian ICUs. Second, given that our study extends over a period of three years, our observational study may potentially lead to changes in clinical practice (i.e., Hawthorne effect) based on the types of questions that ~~are~~ were asked in our case-report forms. Third, some information will only be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

available in subsets of data because not all patients ha~~ved~~ d daily or even weekly laboratory data collected due to resource limitations at our Peruvian ICUs. Fourth, we ~~awere~~ were limited by budget to collect prospective data from only one academic medical center in the United States. Nonetheless, we will also have the opportunity to compare clinical outcomes with those in contemporary multi-center studies (40~~34~~, 41~~35~~). Finally, caution will be needed in applying the results to other LMICs because of differences in healthcare delivery and medical education.

CONCLUSIONS

This study represents a large initiative to establish ~~a~~a n~~N~~etwork of ~~ICUs~~ intensive care units in Peru and understand selected aspects of clinical management and patient-centered outcomes of mechanically ventilated patients. We aim to identify potential aspects of clinical care that can be improved to reduce mortality and decrease length of stay at participating ICUs. The implementation of best practices in resource-limited settings could provide important benefits to patients but also reduce costs. In general, as the economy of any country improves, a larger portion of that country's resources will be diverted towards healthcare, and thus critical care medicine will become more sophisticated. ~~As resources allocated to ICU medicine become more available, the ICU personnel must determine the best way to employ these resources.~~ This study aims to identify ~~differences in~~ clinical ~~treatment~~ practices ~~that account for~~ that may best explain observed differences in patient-centered outcomes~~mortality differences between the ICUs of a developing nation compared to those of the United States.~~ . If the causative agents for major differences in mortality are isolated, protocols directed at their mitigation could result in maximizing lives saved per dollar allocated.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abbreviations: Intensive care unit = ICU; Acute respiratory distress syndrome = ARDS; Chest X-ray; Low- and middle-income countries = LMIC; Medical Intensive Care Unit = MICU; HIC High income countries; Case report form = CRF; Baseline Clinical Information Form = BCI: Daily Clinical Information Form = DCI; Study Termination Form = STF; APACHE II Form = A2F; APACHE III Form = A3F; Mortality Probability Model III Form = MPM; Sequential Organ Failure Assessment Form = SOF; ARDS Follow-up Form = AFF; Sepsis Evaluation Form = SEF; Participant identification code = PID; Emergency Department = ED.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Chalfin DB. Cost-effectiveness analysis in health care. *Hosp Cost Manag Account* 1995;7(4):1-8.
2. Wunsch H, Linde-Zwirble WT, Angus DC et al. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38(10):1947-53.
3. Moerer O, Schmid A, Hofmann M et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. *Intensive Care Med* 2002;28(10):1440-6.
4. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med 2005;33(6):1266-71.
5. Linko R, Suojaranta-Ylinen R, Karlsson S, Ruokonen E, Varpula T, Pettilä V; FINNALI study investigators: One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. *Crit Care 2010*;14(2):R60.
6. Dünser MW, Baelani I, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. *Crit Care Med* 2006;34(4):1234-42.
7. Adhijari N K, Fowler R A, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010;376(9749):1330-46.
8. Esteban A, Anzueto A, Frutos F et al; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287(3):345-55.
9. Fowler RA, Adhikari NK, Bhagwanjee S. Clinical review: critical care in the global context--disparities in burden of illness, access, and economics. *Crit Care* 2008;12(5):225.

Formatted: Numbered + Level: 1 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0" + Indent at: 0.25"

Formatted: Bullets and Numbering

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. *Curr Opin Crit* Care 2012;18(6):700-6.

11. Cooke CR, Kahn JM, Watkins TR, Hudson LD, Rubenfeld GD. Cost-effectiveness of implementing low-tidal volume ventilation in patients with acute lung injury. *Chest* 2009;136(1):79 - 88.

12. Squires DA. Explaining high health care spending in the United States: an international comparison of supply, utilization, prices, and quality. *Issue Brief (Commonw Fund)* 2012;10:1-14.

13. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67:361-370

14. -Brook R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53-72

15. Bysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburg Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Res* 1989; 28(2),193-213

16. Weiss DS, Marmar CR. The Impact of Event Scale - Revised. In: Wilson JP, Keane TM, editors. Assessing Psychological Trauma and PTSD: A Practitioner's Handbook. New York; 1997. pp. 399–411

17. Lopez OL, Kuller LH. Telephone interview for cognitive status. *Neuroepidemiology* 2010;34(1):63-4

18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992 Jun;30(6):473-83.

Formatted: Pattern: Clear

Formatted: Pattern: Clear

Formatted: Pattern: Clear

Formatted: Pattern: Clear

Formatted: Pattern: Clear

Formatted: Pattern: Clear

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

19. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;61(12):1234-4.

20. LeGall Jr, Loirat P, Alpérovitch A. APACHE II – a severity of disease classification system. *Crit Care Med* 1986;14(8):754-5.

21. Knaus WA, Wagner DP, Draper EA et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619-36.

22. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23(10):1638-52

23. Higgins TL, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007;35(3):827-35.

24. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286(14):1754-8.

25. Jahn N, Kaisers UX; American Thoracic Society; European Respiratory Society; European Society of Intensive Care Medicine; Society of Critical Care Medicine; Société de Réanimation de Langue Française. Targeted temperature management in critical care : current 2011 recommendations. *Anaesthesist* 2012;61(6):550-2.

26. Sinuff T, Muscedere J, Adhikari NK et al; for the KRITICAL Working Group, the Canadian Critical Care Trials Group, and the Canadian Critical Care Society: Knowledge Translation

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Interventions for Critically Ill Patients: A Systematic Review. *Crit Care Med* 2013 doi: 10.1097/CCM.0b013e3182982b03.

27. Reinhart K, Perner A, Sprung CL etal; European Society of Intensive Care Medicine: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012;38(3):368-83.

28. Myburgh JA, Finfer S, Bellomo R et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012;367(20):1901-11.

29. Dellinger RP, Levy MM, Rhodes A et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39(2):165-228.

30. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-8.

31. Amato MB, Barbas CS, Medeiros DM et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347-54.

32. Parsons EC, Hough CL, Seymour CW et al; NHLBI ARDS Network. Red blood cell transfusion and outcomes in patients with acute lung injury, sepsis and shock. Crit Care 2011;15(5):R221.

33. Hébert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409-17.

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

Field Code Changed

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

34. Rivers E, Nguyen B, Havstad S et al. Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368-77.

35. Nguyen HB, Corbett SW, Steele R et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007;35(4):1105-12.

36. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP er al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564-75.

37. MacIntyre NR, Cook DJ, Ely EW Jr et al. American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001;120(6 Suppl):375S-95S.

38. Girard TD, Kress JP, Fuchs BD et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. *Lancet* 2008; 371(9607):126-34

39. Ely EW, Margolin R, Francis J et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29(7):1370-9.

Formatted: Font: Times New Roman

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

40. Ali NA, Gutteridge D, Shahul S, Checkley W, Sevransky J, Martin GS. Critical illness outcome study: an observational study of protocols and mortality in intensive care units *Open Access Journal of Clinical Trials* 2011; 3:55-65.

41. Checkley W, Brower R, Korpak A, Thompson BT; Acute Respiratory Distress Syndrome Network Investigators. Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008;177:1215-22.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 1. Flowchart of participating intensive care units.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 2. Sequence of data submission (PCF: Patient Contact Form; BCI: Baseline Clinical Form; DCI: Daily Clinical Form; CXR: Chest X-ray form; SEF: Sepsis Evaluation Form; AFF: ARDS follow-up form; STF: Study Termination Form; RASS: Richmond Agitation-Sedation Scale; 6MWT: 6-minute walk test; PTSD: Post-traumatic stress disorder)

Formatted: Line spacing: Double

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Hospital characteristics and utilization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
Hospital characteristics						
Annual ICU mortality (%)	19.9	20.4	22.9	18.1	16.7	19
Type of hospital	Public (ESSALUD)	Public (ESSALUD)	Public (ESSALUD)	Public (MINSA)	Public (MINSA)	Private, non for profit
Teaching hospital	Yes	Yes	Yes	Yes	Yes	Yes
Critical care training program	Yes	Yes	Yes	Yes	Yes	Yes
Rapid response team	Yes	No	No	No	No	Yes
Electronic patient record	No	No	No	No	No	Yes
Computerized order entry	No	No	No	No	No	Yes
Number of Beds						
Adult beds at hospital	950	1526	1526	800	76	854
Adult ICU beds at hospital	60	69	69	13	16	100
Adult step down beds at hospital	80	114	114	12	6	54
Pediatric ICU beds at hospital	12	9	9	10	0	80
Beds in study ICU	21	24	11	8	11	24
Utilization						
Annual ED visits	140,000	225,300	225,300	71,660	93,000	84,892
Annual hospital admissions	30,000	55,750	55,750	2,685	3,800	48,487
Annual study ICU admissions	300	386	386	200	580	900

Formatted: Width: 11", Height: 8.5"

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Intensive care unit staffing and organization.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU staffing						
Intensivist in ICU	Yes	Yes	Yes	Yes	Yes	Yes
24/7 intensivist	Yes	Yes	Yes	Yes	Yes	No
Leapfrog compliant?	Yes	Yes	Yes	Yes	Yes	Yes
Number of ICU fellows	4	3	2	3	1	2
24/7 ICU fellow	2	0	0	1	0	No
Number of ICU residents	4	1	1	6	1	10
Number of RTs in ICU	0	0	0	0	0	2
Number of ICU nurses	7	11	5	6	4	11
Ratio of beds to nurses	3:1	2.2:1	2.2:1	1.3:1	2.8:1	1.8:1
Number of PAs	0	0	0	0	0	3
Number of NPs	0	0	0	0	0	4
Charge nurse provides patient care?	Yes	Yes	Yes	Yes	Yes	Yes
ICU Organization						
Closed unit	Yes	Yes	Yes	Yes	Yes	Yes

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Has medical director	Yes	Yes	Yes	Yes	Yes	Yes
	Has nurse manager	Yes	Yes	Yes	Yes	Yes	Yes
	Has clinical nurse specialist	No	No	No	No	No	Yes
	CRRT in ICU	Yes	No	No	No	No	Yes

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Process related factors in participating ICUs.

	Hospital Nacional Almenara	Hospital Nacional Rebagliati (ICU-2)	Hospital Nacional Rebagliati (ICU-7)	Hospital Nacional Loayza	Hospital Casimiro Ulloa	Johns Hopkins Hospital
ICU rounding practices						
Pharmacist on rounds	No	No	No	No	No	Yes
Respiratory therapist on rounds	No	No	No	No	No	Yes
Physical therapist on rounds	No	No	No	No	No	Yes
Social worker on rounds	No	No	No	No	No	No
Nutritionist on rounds	No	No	No	No	No	No
Palliative care on rounds	No	No	No	No	No	No
Delirium assessment by nursing	No	No	No	No	No	Yes
Daily goals of care checklist	Yes	No	No	No	Yes	Yes
Daily meeting between physician and charge nurse	Yes	Yes	Yes	Yes	Yes	Yes
Median number of protocols	0	0	0	0	0	19

3

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

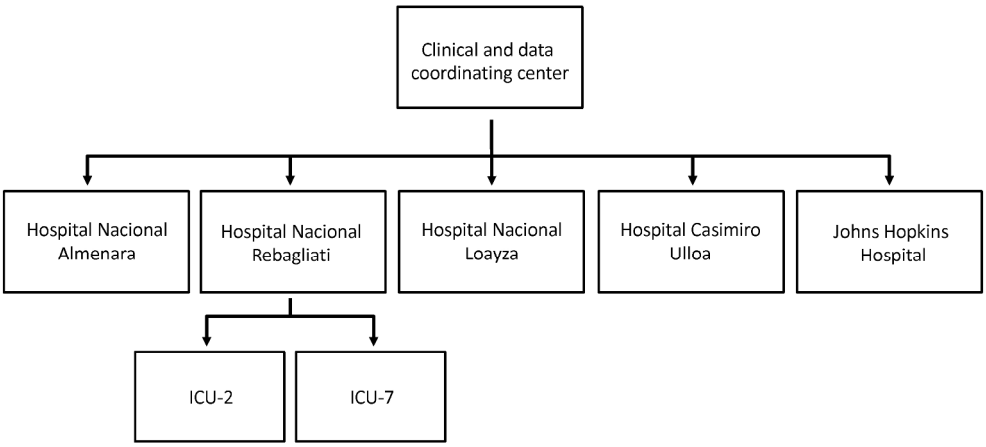

Figure 1.

279x215mm (300 x 300 DPI)

For peer review only

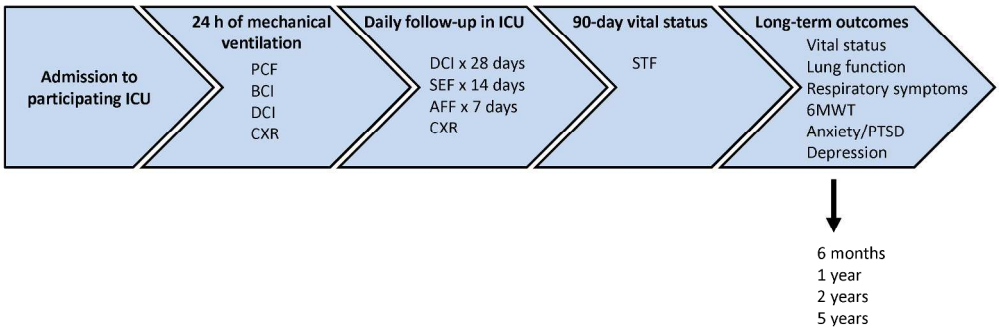

Figure 2.

279x215mm (300 x 300 DPI)

For peer review only