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

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3 **1 Establishment of a prospective cohort of mechanically ventilated patients in five intensive**  
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5 **2 care units in Lima, Peru**  
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**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

## 51 INTRODUCTION

52 Mechanical ventilation has become a mainstay of therapy in the care of critically-ill patients.  
53 Intensive care unit (ICU) practices, mechanical ventilation strategies and their societal costs in  
54 high-income countries (HIC) are well documented. For example, in Germany, Chalfin (1)  
55 calculated that ICU care comprised 20% of hospital costs. In the United States, Wunsch *et al.*  
56 projected that 3% of inpatient hospitalizations required mechanical ventilation in 2005,  
57 comprising 30% of all ICU admissions and accounting for a disproportionate 12% of all hospital  
58 costs (2). Factors contributing to a higher cost of an individual ICU stay include sepsis and  
59 initiation of mechanical ventilation. (3, 4) Despite the higher cost and quality of care that an ICU  
60 setting implies, mortality remains high. In the United States, studies show that approximately  
61 30% of all patients requiring mechanical ventilation die before ICU discharge (2). A Finnish  
62 study estimated a one-year mortality rate of 35% for patients receiving more than 6 hours of  
63 continuous mechanical ventilation (5).

64 In resource-limited settings, however, less is known about clinical practices and  
65 mechanical ventilation strategies used in critically-ill patients (6). Moreover, the burden of  
66 critical illness is higher than generally perceived in low- and middle-income countries (LMICs),  
67 and it is expected to increase with an aging population (6, 7). Esteban *et al.* analyzed data from  
68 361 ICUs in 20 countries across the Americas and Europe and showed a statistically significant  
69 mortality difference between the United States, European, and Latin American ICUs for all  
70 patients receiving mechanical ventilation within a one month period, i.e., 27% vs. 31% vs. 34%,  
71 respectively (8). Their analysis demonstrates that disparities in mortality rates in ICUs of varying  
72 geographical and socioeconomic status exist, but did not address what factors may be

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3 73 contributing to these differences (8). Furthermore, the results from Latin America aggregate data  
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5 74 from countries of varying wealth, which may mask higher mortality rates in poorer settings.  
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8 75 ICUs with fewer resources and greater economic limitations may have essential  
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10 76 differences in delivery of critical care with resulting variations in patient-centered outcomes.  
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12 77 These disparities and their effect are not well understood (6, 9, 10). Implementation of proven  
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14 78 ICU protocols can reduce both mortality and costs (9). Process-driven interventions, such as  
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16 79 standardized protocols of care, could potentially play a large role in minimizing costs while  
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18 80 improving patient outcomes which could be especially advantageous in resource-limited settings  
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20 81 (6, 9). Our study focuses on critically-ill patients receiving mechanical ventilation in LMICs with  
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22 82 significant resource limitations. Our goal is to better understand best practices in resource-  
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24 83 limited settings.  
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29 84 The purpose of this article is to present the design of INTENSIVOS, a prospective,  
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31 85 longitudinal study of mechanically ventilated patients in Lima, Peru. In 2009, Peru spent 5% of  
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33 86 its gross domestic product on healthcare versus 16% in the United States and a median of 10%  
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35 87 across European countries (12). The role of intensive care and mechanical ventilation will  
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37 88 become increasingly important. In this study, we characterize clinical and ventilator management  
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39 89 of patients requiring a minimum of 24 hours of mechanical ventilation in five ICUs in public  
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41 90 hospitals in Peru and one ICU in an academic medical center in the United States. We  
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43 91 hypothesize that measurable differences in patient-centered metrics such as mortality and length  
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45 92 of stay exist between the ICUs in LMICs and the United States. As comparing healthcare  
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47 93 systems internationally can be difficult due to variations in admission criteria, practice and  
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49 94 management, we will adjust mortality by severity of illness upon starting mechanical ventilation  
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51 95 using commonly accepted severity scores and will enroll patients that receive ICU care within a  
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3 96 48-hour window of starting mechanical ventilation. The ultimate goal of the study is to identify  
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6 97 best practices and standardized care tailored to resource-limited settings that will result in  
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8 98 improved patient-centered outcomes and lower costs.  
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3 99 **METHODS**  
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6 100 **Study Objectives**  
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8 101 We seek to characterize 90-day mortality, time spent on mechanical ventilation, ICU and  
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10 102 hospital length of stay, mechanical ventilation strategies and selected aspects of clinical  
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12 103 management of critically-ill patients requiring at least 24 hours of invasive mechanical  
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14 104 ventilation in five ICUs in Lima, Peru and in one ICU in the United States (Figure 1). We  
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16 105 further seek to characterize the proportion of patients admitted to the ICU with acute respiratory  
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18 106 distress syndrome (ARDS) and the proportion of patients who will develop ARDS while in the  
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20 107 ICU. Finally, we will utilize ICU prognostic scores to stratify patients by severity of illness and  
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22 108 compare mortality rates of critically ill patients with those of similar illness severity in  
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24 109 concurrent cohorts of ICU patients in the United States, including the one collected in this study  
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26 110 and in publicly-available datasets. Primary outcomes for this study will be 90-day mortality, time  
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28 111 on mechanical ventilation, ICU and hospital length of stays, and prevalence of ARDS.  
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36 113 **Study Design**  
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38 114 This is a prospective, longitudinal study. At enrollment, we obtained demographics, chronic  
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40 115 disease and acute physiological data for all patients meeting eligibility criteria. We then followed  
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42 116 patients daily to monitor vital status, clinical and ventilator management, acute physiology and  
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44 117 use of sedation during their ICU stay for up to 28 days in the ICU, until ICU discharge or death.  
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46 118 Patients who were successfully discharged from the ICU were followed for vital status during  
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48 119 their inpatient hospital stay. All patients were contacted at 90 days after enrollment to assess vital  
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50 120 status. Survivors in Peru only will be contacted again at 6, 12, 24 and 60 months (long-term  
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52 121 outcomes) after enrollment into the study to assess for vital status. A subset of survivors will be  
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3 122 asked to participate in an ancillary study and undergo a battery of tests at follow-up, including:  
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5 123 questionnaires of quality of life, respiratory symptoms, anxiety, depression and post-traumatic  
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8 124 stress disorder; and, clinical tests including a six-minute walk test, pulmonary function testing  
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11 125 and handgrip strength.

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13 126 We obtained Institutional Review Board (IRB) approval at each of the four participating  
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15 127 hospitals in Lima, Peru: Hospital Nacional Edgardo Rebagliati Martins, Hospital Nacional  
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17 128 Guillermo Almenara Irigoyen, Hospital Nacional Arzobispo Loayza and Hospital de  
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20 129 Emergencias Casimiro Ulloa. In the United States, IRB approval was obtained from the Johns  
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22 130 Hopkins School of Medicine, Baltimore, USA. All IRBs provided a waiver of consent for this  
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25 131 study.

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### 28 29 133 **Eligibility criteria**

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31 134 Eligibility criteria include: 1) age  $\geq 18$  years, 2) at least 24 hours of invasive mechanical  
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34 135 ventilation in one of the ICUs participating in the study and 3) enrollment into the study within  
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36 136 48 hours of onset of mechanical ventilation.

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### 40 41 138 **Study Sites**

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43 139 The study was conducted in five ICUs at four public hospitals of the Social Security System  
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45 140 (ESSALUD) and Ministry of Health (MINSA) in Lima, Peru; and, in the Medical Intensive Care  
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47 141 Unit (MICU) of Johns Hopkins Hospital (Figure 2). We invited only one ICU per hospital with  
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50 142 the exception of Hospital Rebagliati, for which we included two ICUs. Participating ICUs were  
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53 143 selected on the basis of high case volume and willingness to participate. A four-week test period  
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56 144 was initially carried out at each hospital in Peru to determine feasibility and monthly case

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3 145 volume. Of six hospitals approached in Peru, two were unable to meet established *a priori*  
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5 146 requirements during the test period and were not invited to continue in the study.  
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10 148 **Study team**

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12 149 We organized data collection and quality control using a tiered approach. At each ICU, we  
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14 150 identified a team of 2 to 7 study nurses who were responsible for paper-based data collection on  
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16 151 a daily basis and an ICU physician (co-investigators) who supervised data collection and who  
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18 152 were responsible for data quality, review of clinical and ventilator data and interpretation of  
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20 153 chest X-rays (CXR). In addition, a team of two study physician coordinators from the Clinical  
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22 154 and Data Coordinating Center (DCC) oversaw the day-to-day operations of the study and act as  
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24 155 liaisons between the principal investigator and co-investigators. The DCC is composed of team  
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26 156 members located both in Peru and the United States. Study physician coordinators visited each  
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28 157 ICU on average two to three times a week to verify data accuracy and fidelity along with co-  
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30 158 investigators and study nurses, perform range checks and obtain an electronic copy of CXRs.  
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32 159 Incomplete or incorrectly entered case report forms (CRFs) were returned to study nurses for  
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34 160 revision of missing or flagged data. Data forms were collected from all ICUs on a weekly basis  
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36 161 and transferred to the DCC office in Peru for double data entry to a centralized database. The  
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38 162 DCC data manager also conducted a careful review, and incomplete or incorrectly entered CRFs  
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40 163 were returned to the study physician coordinators, who reviewed missed or flagged data with co-  
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42 164 investigators and study nurses. Finally, a DCC nurse was responsible for follow-up telephone  
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44 165 calls to assess vital status after hospital discharge and invited participants to join the long-term  
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46 166 outcomes ancillary study among survivors.  
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## 168 **Case Report Forms**

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

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

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

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3 191 Termination Form (STF). Paper-based worksheets to calculate ICU severity scores such as  
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5 192 APACHE II (A2F), APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA  
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8 193 (SOF) were also provided to the study team. Two additional forms were added later into the  
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10 194 study and will be available in a subset of study participants: ARDS Follow-up Form (AFF), in  
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12 195 which study team members recorded additional ventilator parameters during the first 7 days after  
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14 196 onset in patients that met criteria for ARDS; and, Sepsis Evaluation Form (SEF), which recorded  
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16 197 additional clinical parameters associated with sepsis during the first 14 days after enrollment.  
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20 198 The PCF included patient information such as name, date of birth, address and telephone  
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22 199 contact information for determination of follow-up of vital status after hospital discharge. This is  
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24 200 the only form that contained protected patient information linked to a corresponding unique  
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26 201 participant identification code (PID) in the study. The PCFs are stored in locked cabinets, and the  
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28 202 electronic database is only available to the DCC data manager and to the nurse in charge of  
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30 203 follow-up telephone calls. To complete subsequent forms pertaining to a specific patient, the PID  
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32 204 was transcribed exactly as it appeared on the PCF. PIDs were checked daily by ICU team  
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34 205 members for verification of their accuracy. The PCFs for individual patients serve as the only  
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36 206 link between medical information and patient identifying information, and will be destroyed  
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38 207 upon completion of the study.  
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43 208 The BCI was completed upon patient admission to the ICU. If a patient was readmitted to  
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45 209 the ICU, a new BCI was filled. The BCI collected information in the first 24 hours of mechanical  
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47 210 ventilation. The BCI also recorded height, chronic health information and acute physiology data.  
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49 211 Height was measured following a standardized approach while in supine position. The BCI also  
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51 212 had screening criteria for ARDS modeled after that used by the ARDS Network to assess  
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53 213 whether or not a patient had ARDS upon enrollment.  
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3 214 The DCI was collected daily, considering day 0 as the first 24 hours of mechanical  
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5 215 ventilation. It consisted of daily laboratory tests, selected aspects of clinical management,  
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8 216 mechanical ventilation management, and use of medications such as steroids, sedatives and  
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10 217 antibiotics. DCIs were completed daily for the first 28 days or until patients died or was  
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12 218 discharged from the ICU. Data for the DCI was captured over a defined 24-hour period of time.  
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14 219 To ensure that data was captured only once it was necessary to create an arbitrary 24-hour period  
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16 220 (i.e., a study day). A study day was defined as the 24 hours prior to 8 A.M. on the day of data  
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18 221 collection. Participating hospitals will be instructed to enter data for each DCI using values  
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20 222 obtained as close as possible to 8 A.M.  
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24 223 The STF was used to record 90-day mortality and other ICU milestones such as time on  
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26 224 mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-  
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28 225 hospital deaths were also recorded. Patients were followed throughout their hospital stay after  
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30 226 ICU discharge to determine date of hospital discharge or death. Vital status was assessed in the  
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32 227 STF at 15, 30, 45, 60 and 90 days after initiation of mechanical ventilation. After hospital  
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34 228 discharge, vital status was obtained via a telephone call at 90 days and at subsequent dates as part  
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36 229 of the long-term outcomes sub-study.  
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40 230 Although participating ICUs in Peru are in the process of acquiring the necessary  
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42 231 infrastructure for electronic medical records, none currently have it in place. Thus, data  
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44 232 collectors manually recorded all data in paper-based forms. Although the CRFs had a section to  
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46 233 record CXR findings, digital copies of all corresponding CXR were also obtained and stored.  
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### 51 235 **Sample size**

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53 236 The study spanned a period of three years. We aimed to enroll at least 300 patients at each  
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55 237 participating ICU for a total of 1800 participants across all six ICUs. To detect a difference in  
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3 238 90-day mortality of 10% between a Peruvian ICU and the Johns Hopkins MICU with an  
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6 239 expected baseline mortality of 30%, confidence level of 95% and power 90%, we estimated that  
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8 240 we would need 240 participants per ICU. We chose to over-enroll by 20% to account for  
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10 241 potential missing data.  
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### 15 243 **Characteristics of participating ICUs**

17 244 The five Peruvian ICUs that took part in this study were hosted in four public Peruvian hospitals  
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20 245 of varying size and sources of funding, and thus there are some differences between the number  
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22 246 of beds and influx of patients between units (Table 1). The Hospital Rebagliati, site of two  
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24 247 participating ICUs, is the largest center with over 1,500 beds and more than 55,000 yearly  
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27 248 admissions. Hospital Nacional Almenara and Hospital Nacional Loayza are similar in size, both  
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29 249 with approximately 800 beds and 2,500 yearly admissions. Hospital Casimiro Ulloa is the  
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31 250 smallest center with only 76 beds; however, this is a Trauma and Emergency Medicine center  
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34 251 and thus the number of ED visits and yearly admissions is much higher than would be expected  
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36 252 for a hospital of this size. Annual ICU mortality for all ICUs was quite similar, ranging from  
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38 253 16.7% to 22.9%, and average annual ICU mortality is similar to that of the JHH MICU.  
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### 43 255 **ICU organization and structure**

45 256 The five ICUs in Peru also share several structure (Table 2) and process related factors (Table 3)  
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47  
48 257 in common. They are all closed ICUs with a 24-hour, in-hospital attending intensivist coverage  
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50 258 (vs. the high-intensity, daytime coverage only model at JHH MICU) and with a variable number  
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53 259 of critical care fellows and residents depending on the size of the teaching program. The  
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55 260 Peruvian ICUs average a ratio of 2 beds per nurse (ranging from 1.3:1 to 3:1) and there are  
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3 261 physician assistants or nurse practitioners in the ICU as in the JHH MICU. A notable difference  
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6 262 between the Peruvian ICUs and the JHH MICU is the absence of respiratory therapists in the  
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8 263 former. Since there are no established ventilation protocols in use at the Peruvian ICUs and  
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10 264 ventilator settings are based on intensivist preference. Delirium assessment is not commonly  
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12 265 practiced by ICU nurses in Peru whereas this is standard of care at the JHH MICU. Finally, a  
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15 266 daily goals of care checklist is inconsistently used across participating ICUs in Peru.  
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18 267 Another difference between the Peruvian ICUs and JHH MICU is the presence of a  
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20 268 multi-disciplinary team during rounds (Table 3). Medical rounds the Peruvian ICUs is comprised  
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22 269 only by physicians (attending intensivists, residents and fellows). Nurses do not round with the  
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24 270 medical staff and instead hold their own rounds during shift change. Also, there are no  
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27 271 pharmacists, physical therapists, social workers, nutritionists or palliative care specialists during  
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29 272 rounds. The main communication between nursing and medical staff occurs once a day during a  
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31 273 meeting between the attending physician and charge nurse. Finally, Peruvian ICUs do not have  
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34 274 either electronic patient records or computerized order entry systems as does the JHH MICU.  
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3 276 **DISCUSSION**  
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5 277 This study is designed to characterize patient outcomes and clinical practices in mechanically  
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7 278 ventilated patients in five Peruvian ICUs located at four public hospitals, and to compare with  
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10 279 patients that have a similar distribution in age, sex and severity of illness in an academic medical  
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12 280 center in the United States and, if possible, also with patients enrolled in contemporary multi-  
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14 281 center studies. Specific patient-centered outcomes include 90 day mortality, time on mechanical  
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16 282 ventilation, length of ICU and hospital stay, and prevalence of ARDS. Selected aspects of  
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18 283 clinical management include ventilator management, sedation management, use of laboratory  
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20 284 data to drive clinical decision making among other preventive strategies commonly used in  
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22 285 critical care. We hypothesize that significant differences exist in the management of  
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24 286 mechanically ventilated patients in LMICs and that these differences result in an increased  
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26 287 mortality and a longer length of stay even when adjusted for severity. We aim to identify best  
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28 288 practices and standardized care tailored to resource-limited settings that may result in improved  
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30 289 patient-centered outcomes.  
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36 290 While international comparisons can be notoriously difficult because of inherent  
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38 291 differences in admission criteria and discharge practices across countries, we speculate that  
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40 292 critical care performed in resource-limited settings will likely show negative effects on patient-  
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42 293 centered outcomes. Much of these negative effects are likely driven by limitations of resources.  
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44 294 What is not known is the degree to which these limitations affect patient-centered outcomes and  
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46 295 which specific treatments or interventions are most responsible for these differences. Reasons for  
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48 296 the expected disparity in patient-centered outcomes between LMIC and HIC are likely to be  
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50 297 multifactorial.  
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3 298 What is thought to constitute best practices in critical care around the world and what can  
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5 299 be effectively translated to resource-limited settings? Several critical care societies and  
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8 300 organizations (19-23) have assembled guidelines to help direct and standardize care of critically-  
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10 301 ill patients. Standardization of care can be either structure (i.e., conditions under which patient  
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12 302 care is provided) or process related (i.e., activities that constitute patient care). Structure related  
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14 303 factors, such as availability of nurse and ancillary medical staffing, are generally more difficult  
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16 304 to implement. For example, during implementation of this study, we found that Peru does not  
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18 305 have respiratory therapy practitioners, and ventilator management is done by residents and  
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20 306 attending physicians. Moreover, lack of ancillary services such as social worker and other post-  
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22 307 acute services may have a significant impact on patient-centered outcomes such as length of stay.  
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24 308 Process-related factors may allow for cost-effective interventions through standardization of  
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26 309 clinical management. There is strong evidence-based support of process-based interventions such  
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28 310 as low tidal volumes for lung protective ventilation (24, 25), restrictive blood transfusion  
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30 311 practices (26, 27), early-goal directed therapy (28, 29), conservative fluid management strategies  
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32 312 (30) and standardized sedation management and weaning protocols (31, 32). However, potential  
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34 313 challenges exist with implementation of process-related factors, such as common practices and  
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36 314 beliefs that are institution or country specific.

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39 315 Our study has some potential shortcomings. While the case-report forms implemented in  
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41 316 this study are exhaustive, we were unable to collect information on standardized evaluation tools  
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43 317 for delirium such CAM-ICU (33), which are not used in Peruvian ICUs. Second, given that our  
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45 318 study extends over a period of three years, our observational study may potentially lead to  
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47 319 changes in clinical practice (i.e., Hawthorne effect) based on the types of questions asked in our  
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49 320 case-report forms. Third, some information will only be available in subsets of data because not  
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3 321 all patients had daily or even weekly laboratory data collected due to resource limitations at our  
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5 322 Peruvian ICUs. Fourth, we were limited by budget to collect prospective data from only one  
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8 323 academic medical center in the United States. Nonetheless, we will also have the opportunity to  
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10 324 compare clinical outcomes with those in contemporary multi-center studies (34, 35). Finally,  
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12 325 caution will be needed in applying the results to other LMICs because of differences in  
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14 326 healthcare delivery and medical education.  
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## 19 20 328 **CONCLUSIONS**

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22 329 This study represents a large initiative to establish a Network of ICUs in Peru and understand  
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24 330 selected aspects of clinical management and patient-centered outcomes of mechanically  
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27 331 ventilated patients. We aim to identify potential aspects of clinical care that can be improved to  
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29 332 reduce mortality and decrease length of stay at participating ICUs. The implementation of best  
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31 333 practices in resource-limited settings could provide important benefits to patients but also reduce  
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34 334 costs. In general, as the economy of any country improves, a larger portion of that country's  
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36 335 resources will be diverted towards healthcare, and thus critical care medicine will become more  
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38 336 sophisticated. As resources allocated to ICU medicine become more available, the ICU personnel  
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40 337 must determine the best way to employ these resources. This study aims to identify differences in  
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43 338 treatment that account for mortality differences between the ICUs of a developing nation  
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46 339 compared to those of the United States. If the causative agents for major differences in mortality  
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48 340 are isolated, protocols directed at their mitigation could result in maximizing lives saved per  
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50 341 dollar allocated.  
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3 342 **Abbreviations:** Intensive care unit = ICU; Acute respiratory distress syndrome = ARDS; Chest  
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6 343 X-ray; Low- and middle-income countries = LMIC; Medical Intensive Care Unit = MICU; HIC  
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8 344 High income countries; Case report form = CRF; Baseline Clinical Information Form = BCI:  
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10 345 Daily Clinical Information Form = DCI; Study Termination Form = STF; APACHE II Form =  
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12 346 A2F; APACHE III Form = A3F; Mortality Probability Model III Form = MPM; Sequential  
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15 347 Organ Failure Assessment Form = SOF; ARDS Follow-up Form = AFF; Sepsis Evaluation Form  
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17 348 = SEF; Participant identification code = PID; Emergency Department = ED.  
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22 350 **Other members of the INTENSIVOS Cohort Study:** Maria Alejandra Caravedo, Jorge Cerna,  
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24 351 Long Davalos, Aldo De Ferrari, Maria Alejandra Pereda, Nicole Mongilardi, Navid Shams,  
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8 367 Health. The funding agency had no role in study design or conduct, or in the writing of this  
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10 368 report.  
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15 370 **Conflict of interests:** The authors do not have any conflicts of interest to disclose.  
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20 372 **Authors' contributions:** JD and FC were equally responsible for writing of the manuscript and  
21  
22 373 participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in  
23  
24 374 study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in  
25  
26  
27 375 the design and conduct of this study and assisted in writing of manuscript. WC conceived the  
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29 376 study and had ultimate oversight over study design and conduct, and writing of manuscript  
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**Figure 1. Flowchart of participating intensive care units.**

For peer review only

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3 **Figure 2. Sequence of data submission.**  
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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
<b>Hospital characteristics</b>						
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
<b>Number of Beds</b>						
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
<b>Utilization</b>						
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

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
<b>ICU staffing</b>						
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
<b>ICU Organization</b>						
Closed unit	Yes	Yes	Yes	Yes	Yes	Yes

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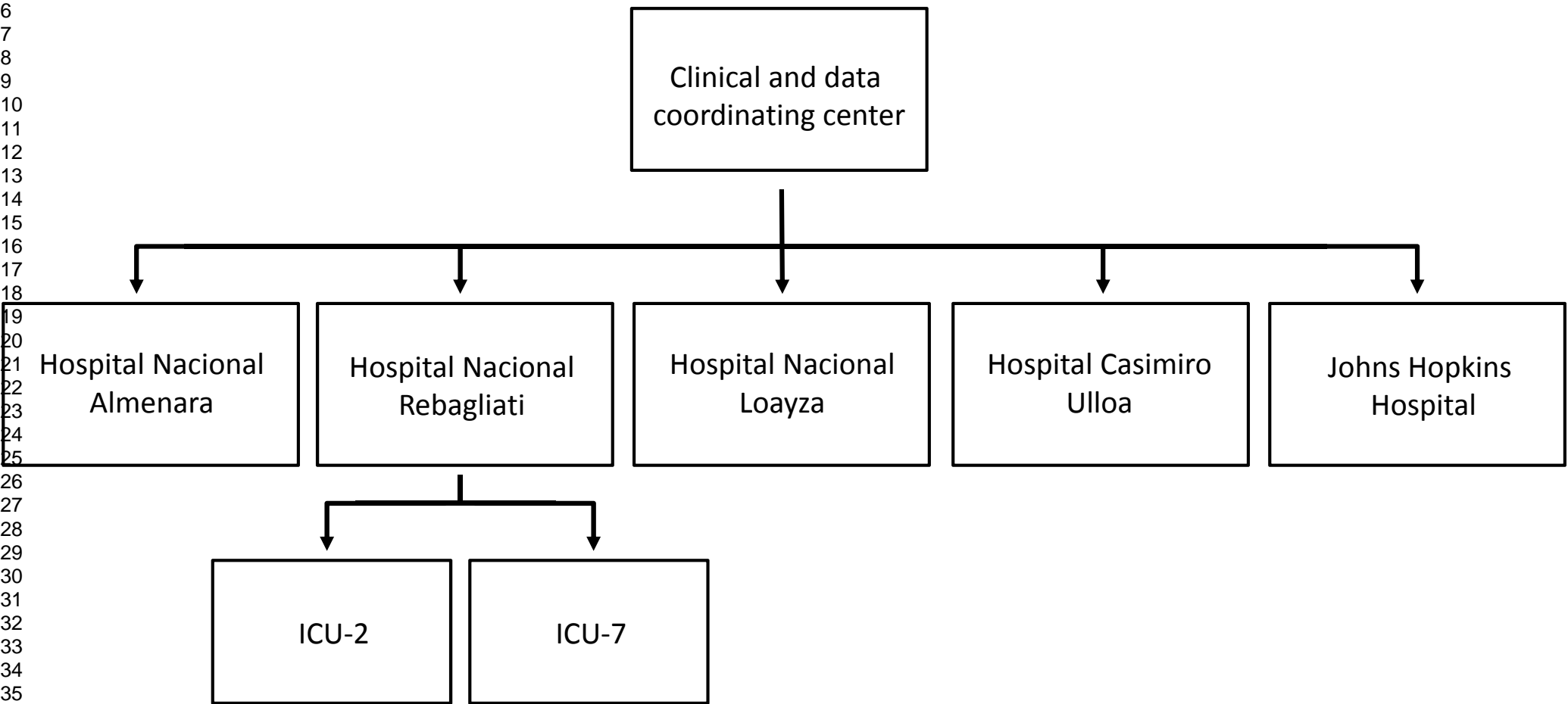
Has medical director	Yes	Yes	Yes	Yes	Yes	Yes
Has nurse manager	Yes	Yes	Yes	Yes	Yes	Yes
Has clinical nurse specialist	No	No	No	No	No	Yes
CRRT in ICU	Yes	No	No	No	No	Yes

For peer review only

**Table 3. Process related factors in participating ICUs.**

	<b>Hospital Nacional Almenara</b>	<b>Hospital Nacional Rebagliati (ICU-2)</b>	<b>Hospital Nacional Rebagliati (ICU-7)</b>	<b>Hospital Nacional Loayza</b>	<b>Hospital Casimiro Ulloa</b>	<b>Johns Hopkins Hospital</b>
<b>ICU rounding practices</b>						
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

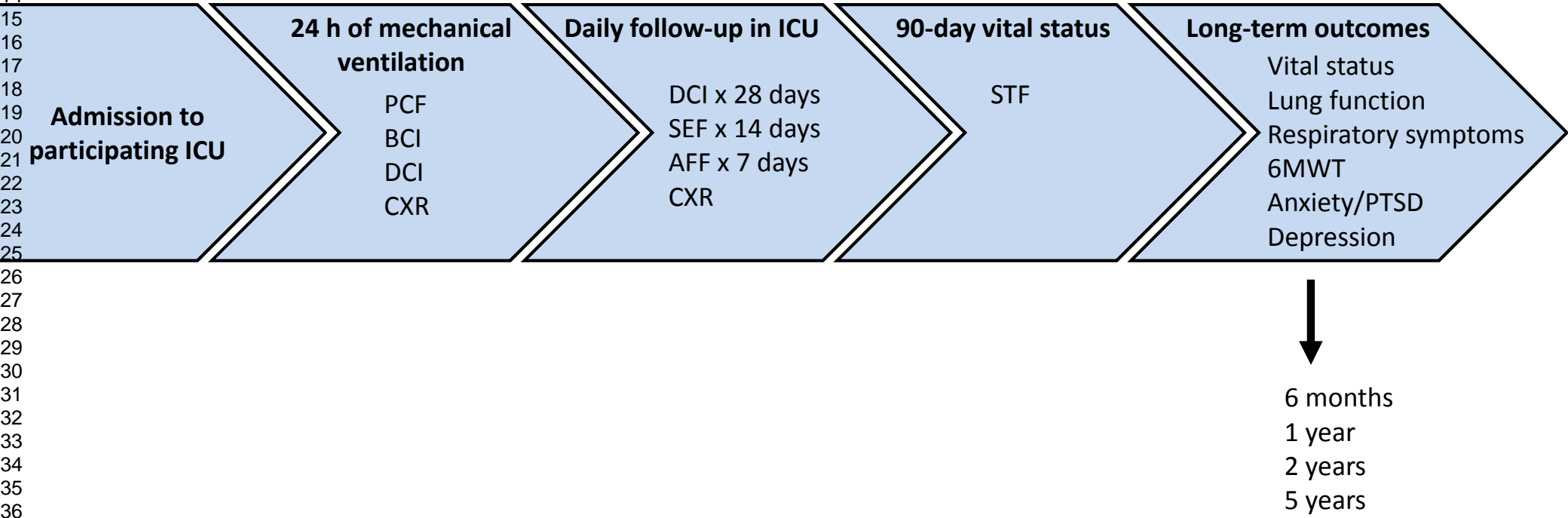
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**Figure 1.**



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**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:	<i>BMJ Open</i>
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
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Manuscripts

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3 **Establishment of a prospective cohort of mechanically ventilated patients in five intensive**  
4 **care units in Lima, Peru: Protocol and organizational characteristics of participating**  
5 **centers**  
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5 study design and conduct, and assisted in writing of manuscript. RB provided expert guidance in  
6 the design and conduct of this study and assisted in writing of manuscript. WC conceived the  
7 study and had ultimate oversight its design and conduct, and writing of this manuscript.  
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## 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.

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3 **Ethics and Dissemination:** We obtained ethics approval at each of the four participating  
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5 hospitals in Lima, Peru and at the Johns Hopkins School of Medicine, Baltimore, USA. Results  
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7 will be disseminated as several separate publications in different international journals.  
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12 **Keywords:** ICU, Critical Care, Outcomes, Protocols, ICU organization  
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## 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



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3 contributing to these differences (8). Furthermore, the results from Latin America aggregate data  
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5 from countries of varying income, which may mask higher mortality rates in poorer settings.  
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8       ICUs with fewer resources and greater economic limitations may have essential  
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10 differences in delivery of critical care with resulting variations in patient-centered outcomes.  
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12 These disparities and their effect are not well understood (6, 9, 10). Implementation of proven  
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14 ICU protocols can reduce both mortality and costs (9). Process-driven interventions, such as  
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16 standardized protocols of care, could potentially play a large role in minimizing costs while  
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18 improving patient outcomes which could be especially advantageous in resource-limited settings  
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20 (6, 9). Our study focuses on critically-ill patients receiving mechanical ventilation in LMICs with  
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22 significant resource limitations. Our goal is to better understand best practices in resource-  
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24 limited settings and identify potential changes that could drive significant improvements in  
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26 outcomes.  
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31       We present the design of a prospective, longitudinal cohort of mechanically ventilated  
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33 patients in Lima, Peru, in five ICUs of public hospitals in Peru and one ICU in an academic  
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35 medical center in the United States. The study was designed to characterize etiologies and  
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37 treatment decisions most frequently seen in mechanically ventilated patients, and their relation  
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39 patient-centered outcomes such as 90-day mortality, time on mechanical ventilation and ICU and  
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41 hospital length of stay. With this information, we aim to identify best practices and standardized  
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43 care strategies that can be tailored to resource-limited settings and applied in the future in these  
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45 ICUs to improve patient-centered outcomes and lower costs.  
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## 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

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

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

## Eligibility criteria

Eligibility criteria were: 1) age  $\geq 18$  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

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

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31 CRFs were modeled after forms used by ARDS Network trials with additional fields added to  
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33 capture the Charlson comorbidity index (19), APACHE II (20), APACHE III (21), MODS (22),  
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35 Mortality Probability Model III (23) and SOFA scores (24). The CRFs were designed to capture  
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37 demographics and chronic health information at baseline and daily information on acute  
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39 physiology, selected aspects of clinical management, mechanical ventilation and weaning  
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41 practices, and sedation management. Forms were originally written in English, translated into  
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43 Spanish and then back-translated into English to confirm accuracy of translation.  
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49 Prior to study start, the study team underwent an in-person training session on how to  
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51 accurately record data in paper-based CRFs. In-person training sessions were repeated  
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53 approximately every six months during the first two years. All study team members were  
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55 provided with a manual of operations with instructions on how to accurately fill the forms. These  
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3 forms were completed in black or blue ink, reviewed by co-investigators and study physician  
4 coordinators and then transferred to the DCC where they were double-data entered into a  
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6 centralized database. The CRFs were: a Patient Contact Form (PCF), Baseline Clinical  
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8 Information Form (BCI), Daily Clinical Information Form (DCI), and a Study Termination Form  
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10 (STF). Paper-based worksheets to calculate ICU severity scores such as APACHE II (A2F),  
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12 APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA (SOF) were also  
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14 provided to the study team. Two additional forms were added later on and are available in a  
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16 subset of study participants: ARDS Follow-up Form (AFF), in which study team members record  
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18 additional ventilator parameters during the first 7 days after onset in patients that met criteria for  
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20 ARDS; and, Sepsis Evaluation Form (SEF), which recorded additional clinical parameters  
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22 associated with sepsis during the first 14 days after enrollment.  
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29 The PCF included patient information such as name, date of birth, address and telephone  
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31 contact information for determination of follow-up of vital status after hospital discharge. This is  
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33 the only form that contained protected patient information linked to a corresponding unique  
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35 participant identification code (PID) in the study. The PCFs were stored in locked cabinets, and  
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37 the electronic database was only available to the DCC data manager and to the nurse in charge of  
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39 follow-up telephone calls. To complete subsequent forms pertaining to a specific patient, the PID  
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41 was transcribed exactly as it appeared on the PCF. PIDs were checked daily by ICU team  
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43 members for verification of their accuracy. The PCFs for individual patients served as the only  
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45 link between medical information and patient identifying information, and will be destroyed  
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47 upon completion of the study.  
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53 The BCI was completed upon patient admission to the ICU. If a patient was readmitted to  
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55 the ICU, a new BCI was filled. The BCI collected information in the first 24 hours of mechanical  
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3 ventilation The BCI also recorded height, chronic health information and acute physiology data.  
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5 Height was measured following a standardized approach while in supine position. The BCI also  
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7 had screening criteria for ARDS modeled after that used by the ARDS Network to assess  
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9 whether or not a patient had ARDS upon enrollment.  
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13 The DCI was collected daily, considering day 0 as the first 24 hours of mechanical  
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15 ventilation. It consisted of daily laboratory tests (complete blood count, comprehensive  
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17 metabolic panel, arterial blood gas results), selected aspects of clinical management (fluid  
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19 management, delirium management, prevention of ventilator-associated pneumonia,  
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21 gastrointestinal ulcers and venous thromboembolism, lung protective ventilation, transfusion  
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23 practices, use of central lines, arterial catheter and pulmonary artery catheters), mechanical  
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25 ventilation management (mode of ventilation, tidal volume, airways pressures, oxygenation and  
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27 PEEP), and use of medications such as vasopressors, medications for prophylaxis for prevention  
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29 of gastrointestinal ulcers and venous thromboembolism, opioids, benzodiazepines, sedatives,  
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31 neuromuscular blockers, anti-psychotics and antibiotics. DCIs were completed daily for the first  
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33 28 days or until patients died or were discharged from the ICU. Data for the DCI was captured  
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35 over a defined 24-hour period of time. To ensure that data was captured only once it was  
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37 necessary to create an arbitrary 24-hour period (i.e., a study day). A study day was defined as the  
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39 24 hours prior to 8 A.M. on the day of data collection. Participating hospitals were instructed to  
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41 enter data for each DCI using values obtained as close as possible to 8 A.M.  
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49 The STF was used to record 90-day mortality and other ICU milestones such as time on  
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51 mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-  
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53 hospital deaths were also recorded. Patients were followed throughout their hospital stay after  
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55 ICU discharge to determine date of hospital discharge or death. Vital status was assessed on the  
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3 STF at 15, 30, 45, 60 and 90 days after initiation of mechanical ventilation. After hospital  
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5 discharge, vital status was obtained via a telephone call at 90 days and at subsequent dates as part  
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7 of the long-term outcomes sub-study.  
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10 Although participating ICUs in Peru are in the process of acquiring the necessary  
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12 infrastructure for electronic medical records, none currently have it in place. Thus, data  
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14 collectors manually record all data in paper-based forms. Although the CRFs have a section to  
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16 record CXR findings, digital copies of all corresponding CXR were also obtained and stored.  
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## 20 21 22 **Sample size**

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24 Enrollment spanned a period of three years. We aimed to enroll at least 300 patients at each  
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26 participating ICU for a total of 1800 participants across all six ICUs.  
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## 30 31 32 **Characteristics of participating ICUs**

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

## 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.

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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

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3 limitations at our Peruvian ICUs. Fourth, we were limited by budget to collect prospective data  
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5 from only one academic medical center in the United States. Nonetheless, we will also have the  
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7 opportunity to compare clinical outcomes with those in contemporary multi-center studies (40,  
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9 41). Finally, caution will be needed in applying the results to other LMICs because of differences  
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11 in healthcare delivery and medical education.  
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## 14 15 16 17 **CONCLUSIONS**

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19 This study represents a large initiative to establish a network of intensive care units in Peru and  
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21 understand selected aspects of clinical management and patient-centered outcomes of  
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23 mechanically ventilated patients. We aim to identify potential aspects of clinical care that can be  
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25 improved to reduce mortality and decrease length of stay at participating ICUs. The  
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27 implementation of best practices in resource-limited settings could provide important benefits to  
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29 patients but also reduce costs. In general, as the economy of any country improves, a larger  
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31 portion of that country's resources will be diverted towards healthcare, and thus critical care  
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33 medicine will become more sophisticated. This study aims to identify clinical practices that may  
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35 best explain observed differences in patient-centered outcomes. If the causative agents for major  
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37 differences in mortality are isolated, protocols directed at their mitigation could result in  
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39 maximizing lives saved per dollar allocated.  
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3 **Abbreviations:** Intensive care unit = ICU; Acute respiratory distress syndrome = ARDS; Chest  
4 X-ray; Low- and middle-income countries = LMIC; Medical Intensive Care Unit = MICU; HIC  
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6 High income countries; Case report form = CRF; Baseline Clinical Information Form = BCI:  
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8 Daily Clinical Information Form = DCI; Study Termination Form = STF; APACHE II Form =  
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10 A2F; APACHE III Form = A3F; Mortality Probability Model III Form = MPM; Sequential  
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12 Organ Failure Assessment Form = SOF; ARDS Follow-up Form = AFF; Sepsis Evaluation Form  
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14 = SEF; Participant identification code = PID; Emergency Department = ED.  
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### 22 **Contributorship Statement**

23  
24 JD and FC were equally responsible for writing of the manuscript and participated in study design  
25 and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ participated in study design and conduct, and  
26 assisted in writing of manuscript. RB provided expert guidance in the design and conduct of this  
27 study and assisted in writing of manuscript. WC conceived the study and had ultimate oversight  
28 over study design and conduct, and writing of manuscript.  
29  
30

### 31 **Competing Interests**

32  
33 None  
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### 38 **FIGURE LEGENDS**

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40 **Figure 1. Flowchart of participating intensive care units.**

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42 **Figure 2. Sequence of data submission** (PCF: Patient Contact Form; BCI: Baseline Clinical  
43 Form; DCI: Daily Clinical Form; CXR: Chest X-ray form; SEF: Sepsis Evaluation Form; AFF:  
44 ARDS follow-up form; STF: Study Termination Form; RASS: Richmond Agitation-Sedation  
45 Scale; 6MWT: 6-minute walk test; PTSD: Post-traumatic stress disorder)  
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**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
<b>Hospital characteristics</b>						
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
<b>Number of Beds</b>						
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
<b>Utilization</b>						
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

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
<b>ICU staffing</b>						
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
<b>ICU Organization</b>						
Closed unit	Yes	Yes	Yes	Yes	Yes	Yes

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

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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
<b>ICU rounding practices</b>						
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

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Establishment of [“INTENSIVOS”](#); a prospective cohort of mechanically ventilated patients in five intensive care units in Lima, Peru: [Protocol and summary of organizational characteristics of participating ICUs centers](#)

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report.

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9 **Conflict of interests:** The authors do not have any conflicts of interest to disclose.  
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12 ~~Authors' contributions~~Contributorship: JD and FC were equally responsible for writing of the  
13 manuscript and participated in study design and conduct. PH, AD, RR, EP, AJ, EC, JP and RQ  
14 participated in study design and conduct, and assisted in writing of manuscript. RB provided  
15 participated in study design and conduct, and assisted in writing of manuscript. RB provided  
16 expert guidance in the design and conduct of this study and assisted in writing of manuscript.  
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18 WC conceived the study and had ultimate oversight ~~over its study~~ design and conduct, and  
19 writing of this manuscript.  
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## 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 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 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. Eligible 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 ~~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 ~~will~~ result in improved patient-centered outcomes and lower costs.

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**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

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## 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

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, ~~aa~~ 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 will characterize clinical ~~and ventilator management of patients requiring a minimum of 24 hours of mechanical ventilation~~ in 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

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~~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.~~

## 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 lengths of stays, 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~~

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~~order to improve patient based outcomes. Finally, a 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 to 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 running of the protocol and conduct of start of this study. At enrollment, we will obtained 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 are were 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 applicable into the study to assess for vital status.~~

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 survivors 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 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 Scale. 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,

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~~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~~were: 1) age  $\geq$ 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 been~~were ~~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

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~~We organized~~ Data 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 were~~ are were responsible for paper-based data collection on a daily basis and an ICU physician (co-investigators) who supervised ~~d~~ data collection and who ~~are were 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) ~~oversee~~ oversee 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~~ visit 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) ~~are were were~~ returned to study nurses for revision of missing or flagged data. Data forms ~~are were 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 ~~conducts~~ conducts ~~ed~~ a careful review, and incomplete or incorrectly entered CRFs ~~are were were~~ returned to the study physician coordinators, who ~~reviewed~~ review missed or flagged data with co-investigators and study nurses. Finally, a DCC nurse ~~is was was~~ responsible for follow-up telephone calls to assess 90-day vital status ~~after hospital discharge and~~ will invite ~~invited~~ invited participants to join the long-term outcomes ancillary study among survivors.

### Case Report Forms

CRFs ~~are were 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

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9 (2145), MODS (2246), Mortality Probability Model III (2347) and SOFA scores (2418). The  
10 CRFs ~~are were~~ were designed to capture demographics and chronic health information at baseline  
11 and daily information on acute physiology, selected aspects of clinical management, mechanical  
12 ventilation and weaning practices, and sedation management. Forms were originally written in  
13 English, translated into Spanish and then back-translated into English to confirm accuracy of  
14 translation.  
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20 ~~Study team members at participating hospitals reviewed and tested Spanish CRFs during~~  
21 ~~the pilot phase. During this pilot, differences in ICU practices between the United States and~~  
22 ~~Peruvian ICUs became apparent and the CRFs were modified to accommodate differences. For~~  
23 ~~example, resource limitations at participating ICUs in Peru limit laboratory data collection to a~~  
24 ~~maximum of once per day per patient, with data frequently being collected less than once per~~  
25 ~~day. Moreover, laboratory tests are usually individually ordered rather than in order sets.~~  
26 ~~Likewise, CXRs are ordered less frequently than in ICUs in the United States.~~  
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34 Prior to study start, the study team underwent an in-person training session on how to  
35 accurately record data in paper-based CRFs. In-person training sessions were repeated  
36 approximately every six months during the first two years. All study team members were  
37 provided with a manual of operations with instructions on how to accurately fill the forms. These  
38 forms were completed in black or blue ink, reviewed by co-investigators and study physician  
39 coordinators and then transferred to the DCC where they were ~~double datae data~~ entered into a  
40 centralized database. The CRFs ~~are were~~ composed of four parts: a Patient Contact Form (PCF),  
41 Baseline Clinical Information Form (BCI), Daily Clinical Information Form (DCI), and a Study  
42 Termination Form (STF). Paper-based worksheets to calculate ICU severity scores such as  
43 APACHE II (A2F), APACHE III (A3F), Mortality Probability Model III (MPM) and SOFA  
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(SOF) ~~have were also been were also~~ provided to the study team. Two additional forms ~~have been were 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 recorded additional ventilator parameters during the first 7 days after onset in patients that ~~meet~~ criteria for ARDS; and, Sepsis Evaluation Form (SEF), which recorded ~~sed ed~~ additional clinical parameters associated with sepsis during the first 14 days after enrollment.

The PCF includes ~~sd ed~~ 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 contains ~~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~~ 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 ~~d~~ as the only link between medical information and patient identifying information, and will be destroyed upon completion of the study.

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

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

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42 The STF ~~was~~ used to record 90-day mortality and other ICU milestones such as time  
43 on mechanical ventilation, dates of tracheostomy placement, and ICU and hospital discharge. In-  
44 hospital deaths ~~are~~ also recorded. Patients ~~are~~ followed throughout their  
45 hospital stay after ICU discharge to determine date of hospital discharge or death. Vital status  
46 ~~was~~ assessed ~~on~~ in the STF at 15, 30, 45, 60 and 90 days after initiation of mechanical  
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ventilation. After hospital discharge, vital status ~~was~~ 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 ~~ed~~ all data in paper-based forms. Although the CRFs ~~have~~ ved a section to record CXR findings, digital copies of all corresponding CXR ~~are~~ 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 ~~take~~ took part in this study ~~are~~ 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

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9 Emergency Medicine center and thus the number of ED visits and yearly admissions is much  
10 higher than would be expected for a hospital of this size. ~~Reported a~~ Annual ICU mortality for all  
11 ICUs was quite similar, ranging from 16.7% to 22.9%, and average annual ICU mortality is  
12 similar to that of the JHH MICU.  
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### 16 17 18 **ICU organization and structure** 19

20 The five ICUs in Peru also share several structure (Table 2) and process related factors (Table 3)  
21 in common. They are all closed ICUs with a 24-hour, in-hospital attending intensivist coverage  
22 (vs. the high-intensity, daytime coverage only model at JHH MICU) and with a variable number  
23 of critical care fellows and residents depending on the size of the teaching program. The  
24 Peruvian ICUs average a ratio of 2 beds per nurse (ranging from 1.3:1 to 3:1) and there are  
25 physician assistants or nurse practitioners in the ICU as in the JHH MICU. A notable difference  
26 between the Peruvian ICUs and the JHH MICU is the absence of respiratory therapists in the  
27 former. Since there are no established ventilation protocols in use at the Peruvian ICUs, ~~and~~  
28 ventilator settings are based on intensivist preference. Delirium assessment is not commonly  
29 practiced by ICU nurses in Peru whereas this is standard of care at the JHH MICU. Finally, a  
30 daily goals of care checklist is inconsistently used across participating ICUs in Peru.  
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41 Another difference between the Peruvian ICUs and JHH MICU is the presence of a  
42 multi-disciplinary team during rounds (Table 3). Medical rounds the Peruvian ICUs ~~are~~ were  
43 comprised only by physicians (attending intensivists, residents and fellows). Nurses do not round  
44 with the medical staff and instead hold their own rounds during shift change. Also, there are no  
45 pharmacists, physical therapists, social workers, nutritionists or palliative care specialists during  
46 rounds. The main communication between nursing and medical staff occurs once a day during a  
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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.

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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 (2549-293) 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 (3024, 3125), restrictive blood transfusion practices (3226, 3327), early-goal directed therapy (3428, 3529), conservative fluid management strategies (360) and standardized sedation management and weaning protocols (374, 382). 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 (393), 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

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9 available in subsets of data because not all patients had ~~ved-d~~ daily or even weekly laboratory data  
10 collected due to resource limitations at our Peruvian ICUs. Fourth, we ~~awere-were~~ limited by  
11 budget to collect prospective data from only one academic medical center in the United States.  
12  
13 Nonetheless, we will also have the opportunity to compare clinical outcomes with those in  
14 contemporary multi-center studies (~~4034, 4135~~). Finally, caution will be needed in applying the  
15 results to other LMICs because of differences in healthcare delivery and medical education.  
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## 21 CONCLUSIONS

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

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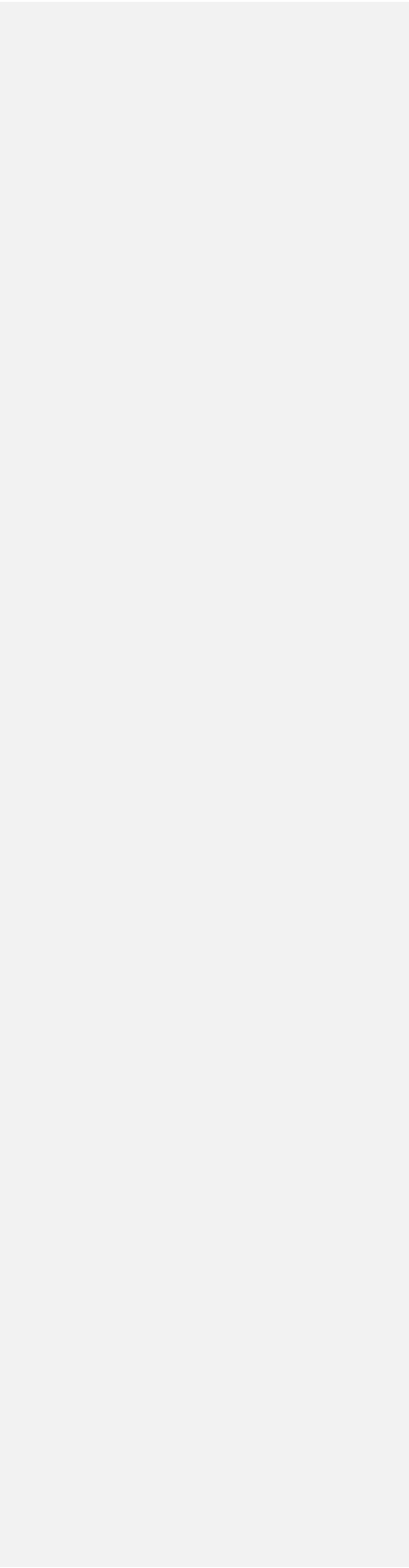
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Figure 1. Flowchart of participating intensive care units.

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**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).

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**Table 1. Hospital characteristics and utilization.**

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

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**Table 2. Intensive care unit staffing and organization.**

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

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<a href="#">Has medical director</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>
<a href="#">Has nurse manager</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>	<a href="#">Yes</a>
<a href="#">Has clinical nurse specialist</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">Yes</a>
<a href="#">CRRT in ICU</a>	<a href="#">Yes</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">No</a>	<a href="#">Yes</a>

For peer review only

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**Table 3. Process related factors in participating ICUs.**

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

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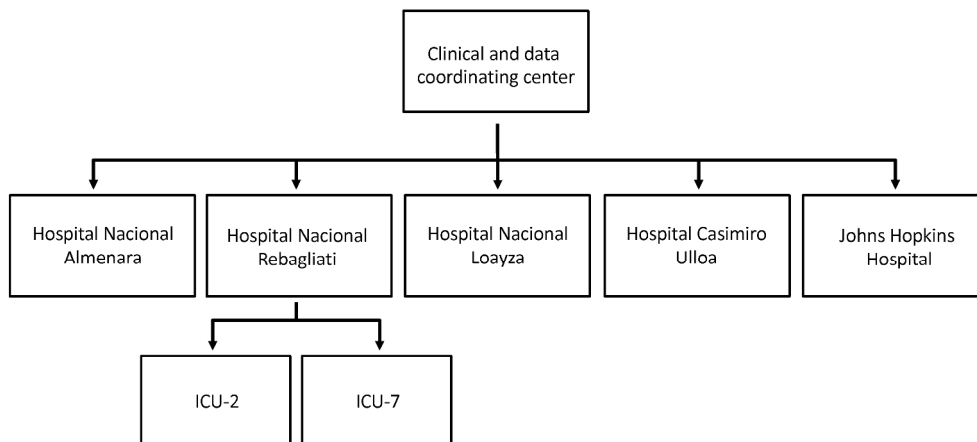
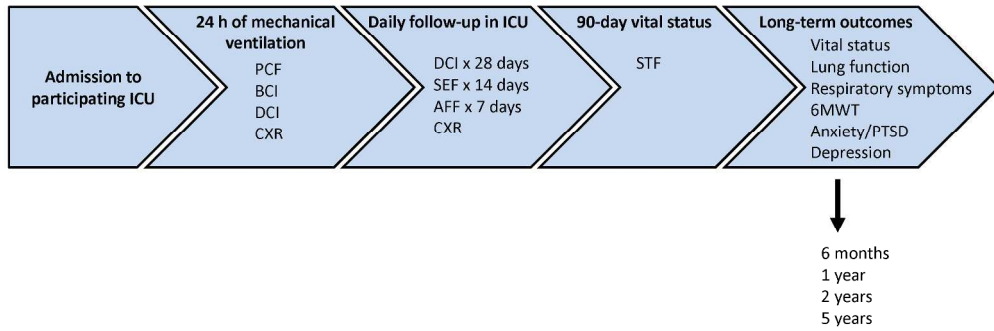


Figure 1.

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**Figure 2.**

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