

# Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome

## A Randomized Clinical Trial

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators

**IMPORTANCE** The effects of recruitment maneuvers and positive end-expiratory pressure (PEEP) titration on clinical outcomes in patients with acute respiratory distress syndrome (ARDS) remain uncertain.

**OBJECTIVE** To determine if lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreases 28-day mortality of patients with moderate to severe ARDS compared with a conventional low-PEEP strategy.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter, randomized trial conducted at 120 intensive care units (ICUs) from 9 countries from November 17, 2011, through April 25, 2017, enrolling adults with moderate to severe ARDS.

**INTERVENTIONS** An experimental strategy with a lung recruitment maneuver and PEEP titration according to the best respiratory-system compliance (n = 501; experimental group) or a control strategy of low PEEP (n = 509). All patients received volume-assist control mode until weaning.

**MAIN OUTCOMES AND MEASURES** The primary outcome was all-cause mortality until 28 days. Secondary outcomes were length of ICU and hospital stay; ventilator-free days through day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; and ICU, in-hospital, and 6-month mortality.

**RESULTS** A total of 1010 patients (37.5% female; mean [SD] age, 50.9 [17.4] years) were enrolled and followed up. At 28 days, 277 of 501 patients (55.3%) in the experimental group and 251 of 509 patients (49.3%) in the control group had died (hazard ratio [HR], 1.20; 95% CI, 1.01 to 1.42;  $P = .041$ ). Compared with the control group, the experimental group strategy increased 6-month mortality (65.3% vs 59.9%; HR, 1.18; 95% CI, 1.01 to 1.38;  $P = .04$ ), decreased the number of mean ventilator-free days (5.3 vs 6.4; difference, -1.1; 95% CI, -2.1 to -0.1;  $P = .03$ ), increased the risk of pneumothorax requiring drainage (3.2% vs 1.2%; difference, 2.0%; 95% CI, 0.0% to 4.0%;  $P = .03$ ), and the risk of barotrauma (5.6% vs 1.6%; difference, 4.0%; 95% CI, 1.5% to 6.5%;  $P = .001$ ). There were no significant differences in the length of ICU stay, length of hospital stay, ICU mortality, and in-hospital mortality.

**CONCLUSIONS AND RELEVANCE** In patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality. These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: [NCT01374022](https://clinicaltrials.gov/ct2/show/study/NCT01374022)

JAMA. 2017;318(14):1335-1345. doi:10.1001/jama.2017.14171  
Published online September 27, 2017.

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**A**cute respiratory distress syndrome (ARDS) is a common clinical problem among critically ill patients and is associated with high mortality and limited long-term quality of life.<sup>1,2</sup> The functional lung size is decreased in ARDS, since many lung units become poorly or nonaerated due to collapse, flooding, or consolidation.<sup>3</sup> This places patients at increased risk of ventilator-induced lung injury due both to overdistention of aerated lung units and cyclic opening and closing of small airways and alveoli (atelectrauma).<sup>4-6</sup>

The aim of recruitment maneuvers and positive end-expiratory pressure (PEEP) titration is to open collapsed lung units and keep them opened, potentially decreasing the risk of atelectrauma. Prospective noncontrolled trials have shown that a lung recruitment maneuver with stepwise increases in PEEP, achieving inspiratory pressures up to 60 cm H<sub>2</sub>O, is able to open most of the collapsed lung tissue in patients with ARDS.<sup>7,8</sup> Two randomized trials<sup>9,10</sup> comparing similar recruitment maneuvers followed by decremental PEEP titration vs a well-established low-PEEP strategy<sup>6</sup> suggested beneficial effects on oxygenation, respiratory-system compliance, and biomarkers of systemic inflammation, without increasing barotrauma or other adverse events. Additionally, systematic reviews evaluating recruitment maneuvers suggested a reduction in mortality, also without increase in barotrauma.<sup>11,12</sup> However, quality of evidence is limited by high risk of bias in most trials and variable use of cointerventions. Thus, the Alveolar Recruitment for ARDS Trial (ART) was conducted to assess whether a strategy of lung recruitment maneuver associated with PEEP titrated according to the best respiratory-system compliance vs a well-established low-PEEP strategy<sup>6</sup> improves clinical outcomes of patients with moderate to severe ARDS.

## Methods

### Study Design and Oversight

We conducted a randomized clinical trial in 120 intensive care units (ICUs) from 9 countries (Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, and Uruguay). The protocol and statistical analysis plan (in [Supplement 1](#)) were published previously.<sup>13,14</sup> Data analysis started after the statistical analysis plan was accepted for publication (see eAppendix in [Supplement 2](#) for details). Ethics committees of all institutions approved the study. Informed consent was obtained from all patients' representatives. An independent data monitoring committee oversaw efficacy and safety data.

### Patients

We enrolled patients receiving invasive mechanical ventilation with moderate to severe ARDS of less than 72 hours of duration. Eligibility was evaluated in 2 phases, a screening and a confirmatory phase. In the screening phase, patients were considered for inclusion in the study if they met the American-European Consensus Conference criteria<sup>15</sup> for ARDS. The exclusion criteria were age younger than 18 years; use of vasoconstrictor drugs in increasing doses over the past 2 hours or mean arterial pressure (MAP) less than 65 mm Hg; contrain-

## Key Points

**Question** Does use of a lung recruitment maneuver associated with positive end-expiratory pressure (PEEP) titration according to the best respiratory-system compliance reduce 28-day mortality of patients with moderate to severe acute respiratory distress syndrome (ARDS) compared with a conventional low-PEEP strategy?

**Findings** In this randomized trial of 1010 patients, 28-day mortality was significantly higher among patients treated with a strategy of lung recruitment and PEEP titration (55.3%) than those treated with a conventional low-PEEP strategy (49.3%).

**Meaning** A strategy using a lung recruitment maneuver and titrated PEEP, in association with volume-assist control ventilation, increased mortality of patients with moderate to severe ARDS.

dications to hypercapnia, such as intracranial hypertension or acute coronary syndrome; pneumothorax, subcutaneous emphysema, pneumomediastinum or pneumatocele; patients in palliative care only; or previously enrolled patients.

Before confirming eligibility, patients received at least 3 hours of mechanical ventilation using a low-PEEP and low-tidal volume strategy proposed by the Acute Respiratory Distress Syndrome Network (ARDSNet).<sup>6</sup> After that, the fraction of inspired oxygen (FIO<sub>2</sub>) was set at 100% and the PEEP at 10 cm H<sub>2</sub>O or more for 30 minutes and arterial blood gases were collected. Eligibility was confirmed if the ratio of the partial pressure (PaO<sub>2</sub>) of oxygen to the FIO<sub>2</sub> (PaO<sub>2</sub>:FIO<sub>2</sub>) was 200 or lower and less than 72 hours had passed since the first time a PaO<sub>2</sub>:FIO<sub>2</sub> ratio of 200 or less was determined.

### Randomization and Masking

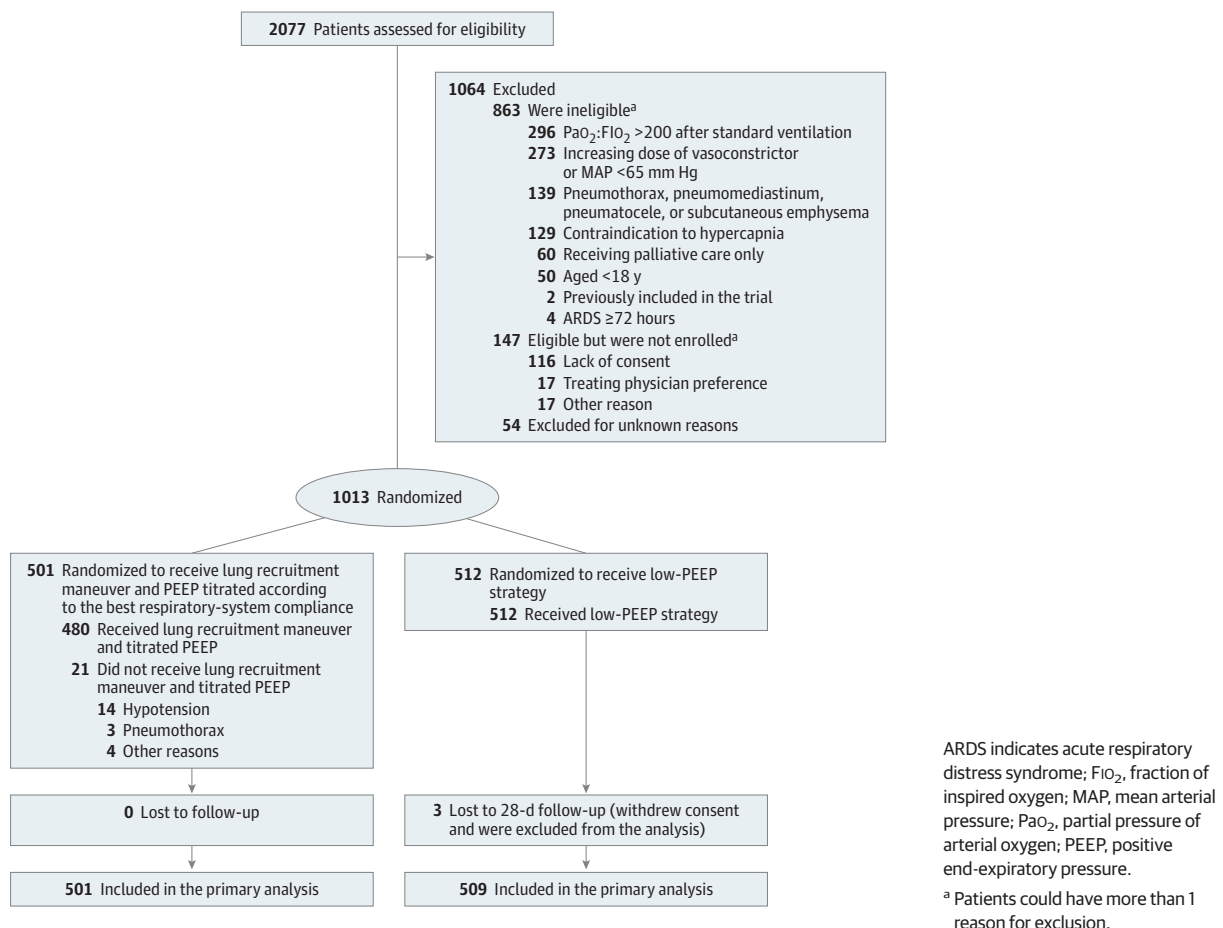
Patients were randomized in a 1:1 ratio to a strategy of lung recruitment associated with PEEP adjusted according to the respiratory-system compliance or to a low-PEEP strategy. The random allocation list was generated by a statistician with no clinical involvement in the trial using a computer-generated random number list. Randomization was conducted with blocks of 4 and stratification by site, age ( $\leq 55$  years or  $> 55$  years) and PaO<sub>2</sub>:FIO<sub>2</sub> ratio ( $\leq 100$  or  $> 100$ ). Allocation concealment was ensured via a central web-based system. The treatment to which a patient was allocated was disclosed only after the patient was enrolled in the study.

Participant, clinicians, and outcome assessors were aware of the assigned treatment.

### Interventions

Patients assigned to the control group continued to receive the low-PEEP strategy.<sup>6</sup> Immediately after randomization, patients assigned to the experimental strategy received a bolus of neuromuscular blocker and hemodynamic status was maintained by administering intravenous fluids when there were signs of fluid responsiveness. Then, we conducted a lung recruitment maneuver with incremental PEEP levels, followed by a decremental PEEP titration according to the best respiratory-system static compliance and by a second recruitment maneuver. The lung recruitment maneuver and PEEP

Figure 1. Flow of Patients in the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial



titration technique were based on those used in previous non-controlled studies.<sup>7,8</sup> After recruitment and PEEP titration, patients were ventilated under volume-assist control mode with PEEP set at the titrated value (the PEEP associated with highest respiratory-system compliance plus 2 cm H<sub>2</sub>O). If PaO<sub>2</sub>:FIO<sub>2</sub> levels were stable or increasing for 24 hours or more after recruitment, weaning of PEEP was started with decreases of 2 cm H<sub>2</sub>O every 8 hours. Apart from the lung recruitment maneuver and PEEP titration scheme, other aspects of care were similar for both groups. The experimental and control group procedures are detailed in the protocol and the manual of operations (Supplements 1 and 3).

Initially, we applied a recruitment maneuver using pressure-controlled ventilation and driving pressure of 15 cm H<sub>2</sub>O. We started with a PEEP of 25 cm H<sub>2</sub>O for 1 minute, then a PEEP of 35 cm H<sub>2</sub>O for 1 minute, and then 45 cm H<sub>2</sub>O for 2 minutes. After recruitment, decremental PEEP titration was started with a PEEP of 23 cm H<sub>2</sub>O in volume-controlled mode. PEEP levels were decreased in steps of 3 cm H<sub>2</sub>O down to a minimum of 11 cm H<sub>2</sub>O. After 4 minutes in each step, we measured respiratory-system static compliance. The PEEP associated with the best compliance plus 2 cm H<sub>2</sub>O was considered the optimal PEEP. After PEEP titration, a new recruitment in pressure-controlled ventilation was conducted in 1 step using PEEP of 45 cm H<sub>2</sub>O for 2 minutes.

In June 2015, starting with the 556th patient, the steering committee, in consultation with the data monitoring committee, decided to modify the recruitment maneuver and PEEP titration strategy after 3 cases of resuscitated cardiac arrest possibly associated with the experimental group treatment were observed. During the recruitment maneuver, PEEP was increased to 25 cm H<sub>2</sub>O, 30 cm H<sub>2</sub>O, and then 35 cm H<sub>2</sub>O, in steps of 1 minute. Maximum plateau pressure was 50 cm H<sub>2</sub>O. Decremental PEEP trial was shorter, with each PEEP step lasting 3 minutes, followed by a new recruitment maneuver with PEEP of 35 cm H<sub>2</sub>O.

### Outcomes

Our primary outcome was mortality until 28 days. Secondary outcomes were length of ICU and hospital stay; ventilator-free days from day 1 until day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; and ICU, in-hospital, and 6-month mortality. We defined as pneumothorax requiring drainage for any case that was possibly due to barotrauma; that is, we did not consider cases judged to be clearly caused by invasive procedures such as central venous puncture or thoracocentesis. We defined as barotrauma within 7 days any pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele of more than 2 cm detected on image examinations between

Table 1. Baseline Characteristics of the Patients

| Characteristic  | Lung Recruitment Maneuver With PEEP Titration Group (n = 501) | Low-PEEP Group (n = 509) |
|---|---|--------------------------|
| Age, mean (SD), y   | 51.3 (17.4)   | 50.6 (17.4)              |
| Women, No. (%)  | 188 (37.5)  | 191 (37.5)               |
| SAPS 3 score, mean (SD) <sup>a</sup>                                      | 63.5 (18.1)   | 62.7 (18.1)              |
| No. of nonpulmonary organ failures, median (IQR)                          | 2 (2-3)   | 2 (2-3)                  |
| Septic shock, No. (%)   | 336 (67.1)  | 331 (65.0)               |
| Cause of ARDS, No. (%)  |   |                          |
| Pulmonary ARDS  | 313 (62.5)  | 313 (61.5)               |
| Pneumonia   | 280 (55.9)  | 276 (54.2)               |
| Gastric aspiration  | 26 (5.2)  | 32 (6.3)                 |
| Lung contusion  | 7 (1.4)   | 4 (0.8)                  |
| Near drowning   | 0   | 1 (0.2)                  |
| Extrapulmonary ARDS   | 188 (37.5)  | 196 (38.5)               |
| Nonseptic shock   | 9 (1.8)   | 12 (2.4)                 |
| Sepsis or septic shock  | 99 (19.8)   | 97 (19.1)                |
| Trauma without lung contusion   | 5 (1.0)   | 5 (1.0)                  |
| Cardiac surgery   | 3 (0.6)   | 0                        |
| Other major surgery   | 20 (4.0)  | 23 (4.5)                 |
| Head trauma   | 4 (0.8)   | 6 (1.2)                  |
| Smoke inhalation  | 4 (0.8)   | 6 (1.2)                  |
| Multiple transfusions   | 8 (1.6)   | 3 (0.6)                  |
| Drug or alcohol abuse   | 1 (0.2)   | 2 (0.4)                  |
| Other   | 35 (7.0)  | 42 (8.3)                 |
| Prone position, No./total No. (%) <sup>b</sup>                            | 31/304 (10.2)   | 30/303 (9.9)             |
| Time since onset of ARDS, median (IQR), h                                 | 15 (7-34)   | 16 (7-30)                |
| Days intubated prior to randomization, median (IQR)                       | 2 (1-4)   | 2 (1-4)                  |
| Respiratory measures, mean (SD)   |   |                          |
| PaO <sub>2</sub> :FIO <sub>2</sub> <sup>c</sup>                           | 119.5 (43.5)  | 117.2 (41.9)             |
| Tidal volume, mL/kg predicted body weight                                 | 5.8 (1.1)   | 5.8 (1.0)                |
| Plateau airway pressure, cm H <sub>2</sub> O                              | 25.8 (4.7)  | 26.2 (5.2)               |
| Minute ventilation, L/min   | 8.9 (2.5)   | 8.9 (2.4)                |
| Respiratory rate, breaths/min   | 25.3 (6.4)  | 25.3 (6.4)               |
| Driving pressure, cm H <sub>2</sub> O <sup>d</sup>                        | 13.5 (4.2)  | 13.5 (4.6)               |
| Positive end-expiratory pressure, cm H <sub>2</sub> O                     | 12.2 (3.0)  | 12.7 (3.3)               |
| Respiratory system static compliance, mL/cm H <sub>2</sub> O <sup>e</sup> | 29.2 (12.4)   | 30.3 (14.4)              |

Abbreviations: ARDS, acute respiratory distress syndrome; FIO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of arterial oxygen; SAPS, Simplified Acute Physiology Score.

<sup>a</sup> The SAPS 3 score can range from 0 to 217, with higher values indicating higher severity of illness.

<sup>b</sup> We started collecting baseline data on prone position from the 407th patient onward.

<sup>c</sup> PaO<sub>2</sub>:FIO<sub>2</sub> at baseline was measured with FIO<sub>2</sub> at 100%.

<sup>d</sup> Driving pressure is the difference between plateau pressure and positive end-expiratory pressure.

<sup>e</sup> Respiratory system static compliance is the ratio of tidal volume to driving pressure.

randomization and 7 days, except those judged to be clearly caused by invasive procedures.

Other exploratory outcomes were death with refractory hypoxemia within 7 days; death with refractory acidosis within 7 days; death with barotrauma within 7 days; cardio-respiratory arrest on day 1; need of commencement or increase of vasopressors or hypotension (MAP<65 mm Hg) within 1 hour after randomization; refractory hypoxemia (PaO<sub>2</sub><55 mm Hg) within 1 hour after randomization; and severe acidosis (pH<7.10) within 1 hour after randomization.

Length of ICU stay (secondary outcome) and all other exploratory outcomes were included in our statistical analysis plan<sup>14</sup> and ClinicalTrials.gov, although they were not originally in our study protocol (see eAppendix in Supplement 2 for details).

### Statistical Analysis

ART was an event-driven study designed to continue until 520 events (28-day deaths) had accrued. This number of events was estimated to provide 90% power, assuming a hazard ratio of 0.75 and type I error of 5%. This hazard ratio is similar to the size of effect used to estimate sample size in other trials in the field.<sup>16,17</sup>

All analyses followed the intention-to-treat principle, considering all patients in the treatment groups to which they were randomly assigned, except for cases lost to follow-up. We carried out complete-case analysis for all outcomes. We planned to conduct sensitivity analysis for the primary outcome using multiple imputation techniques only if follow-up data of 1% or more of the patients was lost. Baseline characteristics were reported as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate. Hypothesis tests were 2-sided. Two interim analyses were performed after recruitment of one-third and two-thirds of the planned sample size to assess effects on clinical outcomes. The data monitoring committee would consider stopping the trial early if there was evidence of harm with 1-sided *P* value <.01. The significance level for the primary outcome final analysis was .042, to maintain overall  $\alpha$  at .05. For all other outcomes, the significance level was .05, without adjustment for multiple comparisons. Because of this, all secondary outcomes and analyses should be interpreted as exploratory.

We assessed the effect of the trial treatments on the primary outcome using Kaplan-Meier curves and calculated the hazard ratio with 95% CI using the Cox proportional hazard model. We conducted 2 sensitivity analyses. The first was a prespecified Cox proportional hazards model adjusted for age, Simplified Acute Physiology Score 3 (SAPS 3) score, and PaO<sub>2</sub>:FIO<sub>2</sub> ratio. The second was a post hoc frailty Cox model with stratification variables (site, age, and PaO<sub>2</sub>:FIO<sub>2</sub>) as random effects.

We used Kaplan-Meier curves and the Cox proportional hazard model to assess the effect of treatment on 6-month survival. We assessed the effects of the intervention on categorical variables with risk ratios and 95% CIs, and we used the  $\chi^2$  test to compare between-group differences. For

continuous outcomes, we estimated the effects of the intervention with generalized linear models using gamma distributions (for lengths of ICU and hospital stay) or a truncated Poisson distribution (for ventilator-free days).

We used Cox proportional hazards to assess interactions between treatment effect and the following prespecified subgroups:  $\text{PaO}_2\text{:FIO}_2$  ( $\leq 100$  vs  $>100$  mm Hg); SAPS 3 score ( $<50$  vs  $\geq 50$ ); pulmonary vs extrapulmonary ARDS; duration of ARDS ( $\leq 36$  hours vs  $>36$  to  $<72$  hours); mechanical ventilation ( $\leq 2$  days, 3-4 days,  $\geq 5$  days); and prone position. As an exploratory analysis, we tested whether treatment effects were similar before and after the protocol amendment of June 2015. We also tested in a post hoc analysis whether treatment effects per quartiles according to order of enrollment in the trial (earlier vs later) were homogeneous. All analyses were performed using the R (R Core Team, 2016) software.

## Results

### Patients

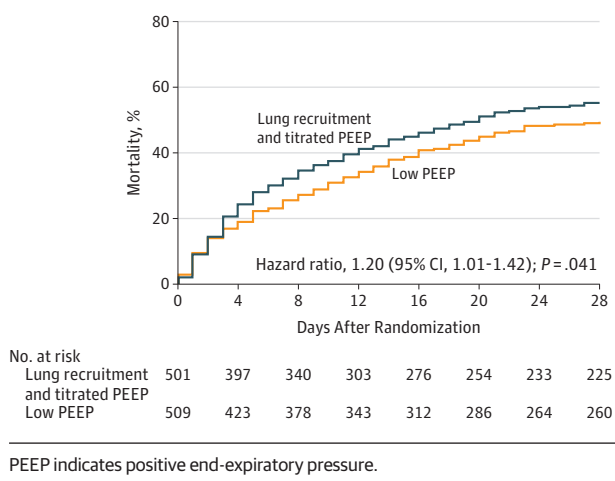
From November 17, 2011, through April 25, 2017, we screened 2077 patients with moderate to severe ARDS. A total of 1064 were not enrolled, of whom 863 (81.1%) met exclusion criteria and 201 (18.9%) were eligible but were not enrolled for other reasons. We randomized 1013 patients, 501 to the lung recruitment strategy and 512 to the low-PEEP strategy. Representatives of 3 patients assigned to the control group withdrew consent to use study data. We obtained 28-day and 6-month follow-up data of all remaining patients, except for 23 who were followed up and censored between 2 and 6 months. Thus, data of 1010 patients (501 in the experimental group and 509 in the control groups) were considered for the final analysis. The data monitoring committee evaluated 2 interim analyses and recommended the trial to be continued. (Figure 1)

Baseline characteristics were well balanced between the study groups (Table 1). Two-thirds of the patients had septic shock. The mean number of nonpulmonary organ failures was more than 2. Most ARDS cases were of pulmonary (62.0%) rather than extrapulmonary origin (38.0%). In the experimental and control groups, baseline (SD) tidal volume and plateau pressures were 5.8 (1.1) and 5.8 (1.0) mL/Kg of predicted body weight, and 25.8 (4.7) and 26.2 (5.2) cm H<sub>2</sub>O, respectively.

### Lung Recruitment

A total of 480 patients (95.8%) in the experimental group received a lung recruitment maneuver after randomization (eTable 1 in Supplement 2). In 78 cases (15.6%) the maneuver had to be interrupted, most often due to hypotension or a decrease in oxygen saturation. In 21 cases, a recruitment maneuver was not attempted due to uncontrolled hypotension (14 cases), detection of pneumothorax (3 cases) after randomization, or other reasons (4 cases). The mean (SD) titrated PEEP was 16.8 (3.8) cm H<sub>2</sub>O. Lung recruitment was repeated after PEEP titration in 393 patients (78.4%). After the initial recruitment and PEEP titration, alveolar recruitment was not re-

**Figure 2. 28-Day Mortality in the Lung Recruitment Maneuver With Titrated PEEP Group vs the Low-PEEP Group**



peated from day 1 to 7 in most patients (62.7%). Conversely, 28 patients in the control group also received a recruitment maneuver within the first 7 days.

### Ventilator Settings and Respiratory Variables

Mean PEEP values from hour 1 through day 7 were higher in the experimental than in the control group (eTable 2 in Supplement 2). Mean values of plateau pressure were also higher in the experimental group, although always below 30 cm H<sub>2</sub>O in both groups. Mean tidal volumes were below 6 mL/kg of predicted body weight in both groups from hour 1 through day 3. The mean  $\text{PaO}_2\text{:FIO}_2$  ratios were higher in the experimental group. Yet decreases in driving pressure from control to experimental group were limited to less than 2 cm H<sub>2</sub>O from day 1 through day 7. Partial pressure of carbon dioxide was higher and arterial pH was lower in experimental group only at the first hour, with values that were not significantly different after day 1.

### Cointerventions

Use of neuromuscular blockers was higher in the experimental than the control group (96.8% vs 73.3%; difference, 23.5%; 95% CI, 19.2%-27.9%;  $P < .001$ ), reflecting the protocol requirement for their use before the recruitment maneuver (eTable 3 in Supplement 2). The proportion of patients who received sedatives on any day was higher in the experimental group (99.0% vs 97.1%; difference, 1.9%; 95% CI, 0.0%-3.9%;  $P = .05$ ), although there was no difference between groups in the median number of days receiving sedatives. There were no differences among groups in other cointerventions or on the need of rescue therapies for hypoxemia.

### Outcomes

At 28 days, there were 277 deaths (55.3%) among 501 patients in the experimental group and 251 deaths (49.3%) among 509 patients in the control group, with a hazard ratio of 1.20 (95% CI, 1.01-1.42;  $P = .041$ ) (Figure 2). After adjustment for baseline covariates, age, SAPS 3, and  $\text{PaO}_2\text{:FIO}_2$ , the hazard ratio for

Table 2. Outcomes Among Patients Treated With Lung Recruitment Maneuver With Positive End-Expiratory Pressure (PEEP) vs Low-PEEP Strategy

| Outcome  | Lung Recruitment Maneuver With PEEP Titration Group (n = 501) | Low-PEEP Group (n = 509) | Type of Effect Estimate | Effect Estimate (95% CI) | P Value |
|--|---|--------------------------|-------------------------|--------------------------|---------|
| <b>Primary Outcome</b>   |   |                          |                         |                          |         |
| Death ≤28 d, No. of events/total No. (%)   | 277/501 (55.3)  | 251/509 (49.3)           | HR                      | 1.20 (1.01 to 1.42)      | .041    |
| <b>Secondary Outcomes</b>  |   |                          |                         |                          |         |
| Death, No. of events/total No. (%)   |   |                          |                         |                          |         |
| In intensive care unit   | 303/500 (60.6)  | 284/509 (55.8)           | RD                      | 4.8 (-1.5 to 11.1)       | .13     |
| In hospital  | 319/500 (63.8)  | 301/508 (59.3)           | RD                      | 4.5 (-1.7 to 10.7)       | .15     |
| Within 6 mo <sup>a</sup>   | 327/501 (65.3)  | 305/509 (59.9)           | HR                      | 1.18 (1.01 to 1.38)      | .04     |
| Length of stay, d  |   |                          |                         |                          |         |
| Intensive care unit, mean (SD)   | 18.2 (22.4)   | 19.2 (25.9)              | MD                      | -1.0 (-4.0 to 2.0)       | .51     |
| Median (IQR)   | 12.0 (5.0 to 23.0)  | 14.0 (7.0 to 23.0)       |                         |                          |         |
| Hospital, mean (SD)  | 25.5 (32.3)   | 26.2 (31.7)              | MD                      | -0.7 (-4.6 to 3.3)       | .74     |
| Median (IQR)   | 15.0 (5.0 to 32.0)  | 18.0 (7.0 to 35.0)       |                         |                          |         |
| No. of ventilator-free d from d 1 to d 28, mean (SD), d                                    | 5.3 (8.0)   | 6.4 (8.6)                | MD                      | -1.1 (-2.1 to -0.1)      | .03     |
| Median (IQR)   | 0.0 (0.0 to 11.0)   | 0.0 (0.0 to 14.0)        |                         |                          |         |
| Pneumothorax requiring drainage ≤7 d, No./total No. (%)                                    | 16/501 (3.2)  | 6/509 (1.2)              | RD                      | 2.0 (0.2 to 3.8)         | .03     |
| Barotrauma ≤7 d, No./total No. (%)   | 28/501 (5.6)  | 8/509 (1.6)              | RD                      | 4.0 (1.5 to 6.5)         | .001    |
| <b>Exploratory Outcomes, No./Total No. (%)</b>   |   |                          |                         |                          |         |
| Death  |   |                          |                         |                          |         |
| Within 7 d   | 160/501 (31.9)  | 130/509 (25.5)           | RD                      | 6.4 (0.6 to 12.2)        | .03     |
| With refractory hypoxemia ≤7 d <sup>b</sup>  | 45/501 (9.0)  | 51/509 (10.0)            | RD                      | -1.0 (-4.9 to 2.8)       | .59     |
| With refractory acidosis ≤7 d <sup>c</sup>   | 68/501 (13.6)   | 56/509 (11.0)            | RD                      | 2.6 (-1.7 to 6.8)        | .25     |
| With barotrauma ≤7 d <sup>d</sup>  | 7/501 (1.4)   | 0/509 (0.0)              | RD                      | 1.4 (0.2 to 2.6)         | .007    |
| Cardiorespiratory arrest on day 1 <sup>e</sup>   | 5/501 (1.0)   | 2/509 (0.4)              | RD                      | 0.6 (-0.6 to 1.8)        | .28     |
| Need of commencement or increase of vasopressors or hypotension (MAP <65 mm Hg) within 1 h | 174/500 (34.8)  | 144/508 (28.3)           | RD                      | 6.5 (0.5 to 12.4)        | .03     |
| Refractory hypoxemia (Pao <sub>2</sub> <55 mm Hg) ≤1 h                                     | 8/496 (1.6)   | 10/506 (2.0)             | RD                      | -0.4 (-2.2 to 1.5)       | .81     |
| Severe acidosis (pH<7.10) ≤1 h   | 65/496 (13.1)   | 55/506 (10.9)            | RD                      | 2.2 (-2.0 to 6.5)        | .29     |

Abbreviations: HR, hazard ratio; IQR, interquartile range; MAP, mean arterial pressure; MD, mean difference; RD, risk difference.

<sup>a</sup> Six-month follow-up data was obtained from all patients, except for 23 cases who were followed up and censored between 2 and 6 mo.

<sup>b</sup> Death with refractory hypoxemia defined as death with last arterial blood gas analysis before dying collected with Fio<sub>2</sub> = 100% showing Pao<sub>2</sub><55 mm Hg.

<sup>c</sup> Death with refractory acidosis defined as death with last arterial blood gas analysis before dying with pH<7.10.

<sup>d</sup> Death with barotrauma defined as persistent pneumothorax or expanding subcutaneous emphysema or persistent pneumomediastinum with chest tube at the involved site.

<sup>e</sup> Cardiorespiratory arrest defined as unexpected cardiac arrest, not due to progressive refractory shock.

28-day mortality was 1.22 (95% CI, 1.03-1.45;  $P = .02$ ). In the post hoc frailty Cox model, the hazard ratio was 1.21 (95% CI, 1.02-1.44;  $P = .03$ ).

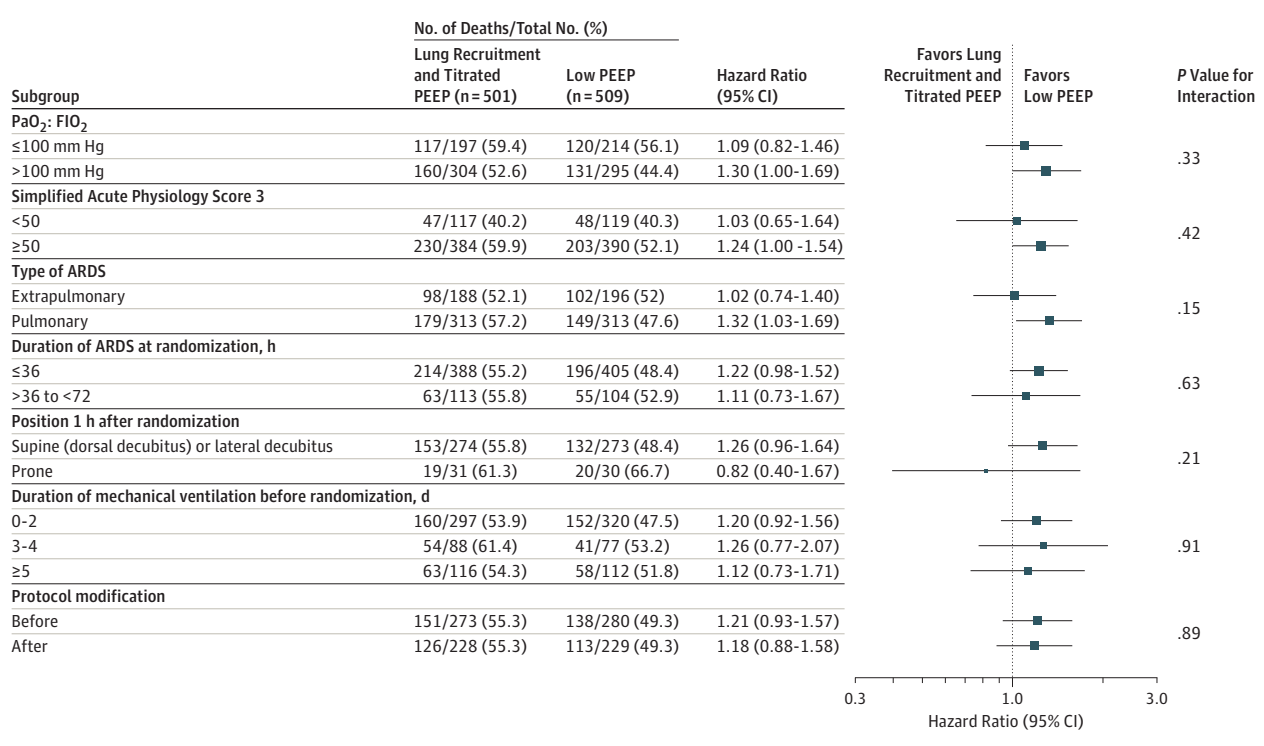
All-cause mortality was also higher within 6 months in the experimental than in the control group (65.3% vs 59.9%; hazard ratio, 1.18; 95% CI, 1.01-1.38;  $P = .04$ ) (Table 2). Differences in the ICU or in-hospital mortality between groups were not statistically significant. Compared with the control group, mortality in the experimental group was higher during the first 7 days, with increased rates of death with barotrauma (Table 2). There were no significant differences in the rates of death with refractory hypoxemia, death with acidosis, and cardiorespiratory arrest between groups. Lengths of stay in the ICU or hospital were also not significantly different. The experimental group had fewer ventilator-free days during the first 28 days. The rates of pneumothorax requiring

drainage and rates of any barotrauma increased in the experimental group. Within 1 hour, commencement or increase in vasopressors or hypotension were more common in the experimental group, but there were no differences in refractory hypoxemia or severe acidosis.

### Subgroup and Exploratory Analyses

Effects of experimental vs control strategy on 28-day mortality were not significantly different across subgroups (Figure 3). Treatment effects were also not significantly different in the periods of study before and after the protocol was modified with reduction in the length and in the maximum PEEP and pressure levels of the recruitment maneuver ( $P = .89$ ). Treatment effects were also not significantly different per quartiles according to order of enrollment in the trial ( $P = .76$ ).

Figure 3. Effects of the Lung Recruitment Maneuver With Titrated PEEP vs the Low-PEEP Group on Mortality According to Subgroups



The size of data markers is proportional to the inverse of variance. Protocol modification indicates the modification in the experimental group strategy after the 556th patient, with decreases in the pressures and duration of the recruitment maneuver.

ARDS indicates acute respiratory distress syndrome; FIO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

## Discussion

In this trial enrolling adults with moderate to severe ARDS, a strategy of lung recruitment and PEEP titration according to the respiratory-system compliance increased 28-day mortality compared with an established low-PEEP strategy. In addition, the lung recruitment strategy increased 6-month mortality, the risk of any barotrauma and death with barotrauma, and the need for vasopressors or hypotension in the first hour. Conversely, the lung recruitment strategy decreased the number of days free of mechanical ventilation during 28 days.

One potential explanation for the findings of this trial relates to an unfavorable balance between potential positive (reduction in driving pressure)<sup>10</sup> and negative (increase in overdistention, hemodynamic impairment)<sup>18,19</sup> physiological consequences of lung recruitment and PEEP. Although some studies showed almost full opening of collapsed alveoli after recruitment maneuvers achieving high inspiratory pressures,<sup>7,8</sup> only mild responses were observed in this trial as suggested by the small increments in the respiratory-system compliance and reductions in driving pressure. Furthermore, the driving pressure, a strong predictor of survival in ARDS,<sup>20,21</sup> decreased by a mean of only less than 2 cm of water. On the contrary, the risk of barotrauma within 7 days and signs of hemodynamic impairment within 1 hour

increased in the experimental group, suggesting lung injury and hemodynamic impairment as mechanisms that may have driven increased mortality. Nevertheless, the incidence of barotrauma, even in the experimental group, was lower than in any previous studies using high PEEP levels.<sup>22</sup>

Another potential explanation for the results observed in this trial lies in the lung protective characteristics of the control group, which may have offset any potential physiological advantages of the lung recruitment and PEEP titration strategy. The control group strategy called for a tidal volume of 6 mL/kg (or less if plateau pressure was >30 cm H<sub>2</sub>O) and use of lower PEEP levels.<sup>6</sup> Adherence to low tidal volume was very strict, with lower mean tidal volumes than the ARDSNet trials.<sup>6,23</sup> Conversely, PEEP values were approximately 3 cm H<sub>2</sub>O higher than that observed in control groups from previous studies.<sup>22</sup> The use of strictly low tidal volumes and resulting low driving pressures may have reduced lung injury due to tidal overdistention. Furthermore, intermediate levels of PEEP may have contributed to maximizing homogeneity and preventing atelectrauma.

A third possible explanation for the findings of this trial is the breath stacking phenomenon, which may occur inadvertently in patients receiving protective ventilation, especially in the volume-assist control mode and with low tidal volumes.<sup>24,25</sup> It was documented in 1 patient enrolled in the experimental group and routinely monitored with electrical impedance tomography (eFigure 1 in Supplement 2).

The patient received 12 mL/kg of effective tidal volume in more than 40% of the breaths, whereas the ventilator displayed 6 mL/kg. Although the incidence of this phenomenon was likely similar in both groups, it may have caused more lung overstretch with disproportionately higher driving pressures in patients submitted to higher PEEP levels.

The choice of the ARDSNet table of lower instead of higher PEEP values for the control group in this trial might be questioned, since an individual patient data meta-analysis suggested a survival benefit for higher PEEP levels in the subgroup of patients with moderate to severe ARDS.<sup>22</sup> Three main reasons supported the option for lower PEEP values. First, the meta-analysis did not show benefit of high PEEP for the overall group of patients with ARDS.<sup>22</sup> Second, none of the individual trials showed a significant effect on mortality.<sup>17,23,26</sup> Third, the trials included in the meta-analysis used substantially different strategies both in the experimental and control groups, with variable use of recruitment maneuvers. Therefore, it is uncertain whether the potential benefit was due to higher PEEP or to the lung recruitment maneuver itself.

This trial has strengths. Bias was controlled by using concealed allocation, intention-to-treat analysis, and by avoiding losses to follow-up. Analyses were based on a large number of events, which allowed for adequate random error control. Patient eligibility was confirmed only after ventilation with a lung protective low-tidal volume strategy and standardized FIO<sub>2</sub> and PEEP settings before collecting arterial blood gases. Except for the lung recruitment maneuvers and PEEP titration scheme, identical mechanical ventilation protocol with low-tidal volume was applied for both groups. In addition, the study involved centers from 9 countries, which contributes to generalizability of its results.

### Limitations

This study has several limitations. First, it was not feasible to blind participants, clinicians, and outcome assessors. It is possible that processes of care might have been affected by

knowledge of treatment allocation. Conversely, blinding would not affect classification of the primary outcome. Second, it was not possible to classify enrolled patients into ARDS subphenotypes, which may respond differently to therapies such as PEEP.<sup>27,28</sup> Determination of subphenotype requires collecting plasma samples to perform analysis of biomarkers; however, this was not conducted due to funding restrictions. Third, it has been suggested that baseline responsiveness to a test of PEEP elevation predicts percentage of potentially recruitable lung and the clinical response to a strategy of lung recruitment associated with high PEEP.<sup>29,30</sup> However, since responsiveness to PEEP at baseline was not assessed, it is not possible to analyze whether this characteristic modifies treatment effect. Nevertheless, there was no evidence of heterogeneity of treatment effect in any of the subgroups examined. Fourth, patients were enrolled in the trial over 6 years. The care of patients with ARDS may have changed during this period, which might have affected results. However, an analysis of treatment effects on mortality according to order of enrollment provides no evidence that effects changed over time. Fifth, a strategy involving lung recruitment and PEEP titration (primary interventions) is complex in the sense that not only the primary interventions are part of it, but also cointerventions that need to be aggregated. For example, administering neuromuscular blockers and fluids in preparation for the recruitment maneuver. As a consequence, it is not possible to ascribe observed clinical effects exclusively to the direct effects of lung recruitment maneuver and PEEP.

### Conclusions

In patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality. These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients.

### ARTICLE INFORMATION

**Accepted for Publication:** September 1, 2017.

**Published Online:** September 27, 2017.  
doi:10.1001/jama.2017.14171

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. All authors received grant support from Program to Support Institutional Development of Universal System (PROADI) from the Brazilian Ministry of Health to conduct the study. Dr Amato also received grants from Timpel S. A. and Medtronic. No other disclosures are reported.

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Rafael Alexandre O. Deucher, and Francine Castro Escobar Furlan; *Instituto de Infectologia—Emílio Ribas*: Fabrício Rodrigues Torres de Carvalho, Roberto Muniz Jr, Hélio Penna Guimarães, and Lucia Conceição Andrade; *Instituto do Câncer do Estado de São Paulo—ICESP*: Ludmila Abrahão Hajjar, Filomena Regina Barbosa Gomes Galas, and Juliano Pinheiro de Almeida; *Irmandade da Santa Casa de Misericórdia de São Paulo*: Roberto Marco, Elzo Peixoto, Fabiano Hirata, and Chen Yen Ju; *MEDIMIG*: Bruno Bonaccorsi Fernandino, Daniel Lage de Assis Rocha, and Nathalia Azzi Barbosa; *Santa Casa da Misericórdia de Ouro Preto*: Janine Dias Alves, Ludmila Furtado Lamego, and Juliana Maria de Linhares; *Santa Casa de Caridade de Diamantina*: Marcelo Ferreira Sousa, Marcia Maria Ferreira de Souza, Fernanda Luiza Guimarães de Carvalho, and Monica Aparecida Leite; *Santa Casa de Maringá*: Paulo Torres, Daniel Bolognese, and Valintin Lacerda; *Sociedade Brasileira de Amparo a Saúde (SOBRASA)*: Giovanni Cisari, Alexandre Souza Marques, Alex Amarante Costa, and Leonardo Bonin Campos; *Unidade de Emergência do Hospital das Clínicas da FMRP-USP*: Marcos de Carvalho Borges, Wilson José Lovato, Bruno Guimarães Dantas, Débora Ribeiro Campos, Larissa Christina Pires Barriento, Vivian Rossi Peras Américo, Thatiana Barboza Carnevali Bueno, Daniela Morales, Tania Mara Gomes, and Rodrigo Barbosa Cerantola; *UTI Central da Irmandade Santa Casa de Misericórdia de Porto Alegre*: Roselaine Pinheiro de Oliveira, Cassiano Teixeira, and Jorge Höher; *UTIs da Anestesiologia, da Emergência Cirúrgica e Gastroenterologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP)*: Luiz Marcelo Sá Malbouisson, Filipe Matheus Cadamuro, Estevão Bassi, Rafaella Maia, João Alexandre Dias e Santos, Catherine Oliveira, Ana Paula Balzi, Paulo Tierno, and Guilherme Marques Andrade; *UTI Clínica do Hospital São Paulo da Universidade Federal de São Paulo (UNIFESP)*: Renato Delascio Lopes, Marcos Cesar Ramos Mello, Hélio Penna Guimarães, and Leticia Sandre Vendrame; *UTI da Disciplina de Anestesiologia, Dor e Terapia Intensiva do Hospital São Paulo da Universidade Federal de São Paulo (UNIFESP)*: Flávia Ribeiro Machado, Heloisa Baccaro Rossetti Santana, Alessandro de Carvalho Jr, Vanessa Marques Ferreira Mendez, Walkyria de Araujo Macedo Pinto, Renata dos Santos Francisco, Flavio Steponovicus Piedade Cruz, Abigail Silva de Araujo, Alda Paiva de Souza, and Tuanny Teixeira Pinheiro; *UTI de Emergências Clínicas do Hospital de Clínicas da Universidade Estadual de Campinas (UNICAMP)*: Thiago Martins Santos, Carolina Matida Gontijo-Coutinho, Daniel Franci, and Marco Antonio de Carvalho-Filho; *UTI de Queimados do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP)*: Amanda Maria Ribas Rosa de Oliveira and João Manoel Silva Jr; *UTI do Hospital Santa Rita—Irmandade Santa Casa de Misericórdia de Porto Alegre*: Thiago Costa Lisboa, André Peretti Torelly, Alldren Silva de Souza, and Martha Hadrich; *UTI do Pavilhão Pereira Filho da Irmandade Santa Casa de Misericórdia de Porto Alegre*: Patricia Schwarz, Paula Berto and José Augusto Santos Pellegrini; *UTI do Pronto Socorro do Hospital São Paulo da Universidade Federal de São Paulo (UNIFESP)*: Aécio Flavio Teixeira de Gois, Moacyr Silva Jr, Paulo Gessolo Lins, and Eulália Priscila Cavalcante Lola Biazotto; *UTI Geral dos Adultos do Hospital de Clínicas da Universidade Estadual de Campinas (UNICAMP)*: Desanka

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**Funding/Support**: This study was funded by and conducted as part of the Program to Support Institutional Development of Universal System (PROADI) from the Brazilian Ministry of Health. The trial was coordinated by the HCor Research

Institute and endorsed by the Brazilian Research in Intensive Care Network (BRICNet).

**Role of the Funder/Sponsor:** The funding sources had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Reproducible Research Statement:** We will share the database containing deidentified individual participant data, data dictionary documentation, statistical analysis plan, and analysis code. Beginning 6 months and ending 24 months following article publication, the trial steering committee will evaluate proposals of studies accompanied by a statistical analysis plan and may grant access to the data for approved proposals. After 24 months, the database and accompanying documents will be publicly available in an institutional data repository (<http://www.hcor.com.br>).

**Additional Contributions:** We thank the Brazilian Association of Intensive Care Medicine for assisting with facilitating invitation to Brazilian intensivists. We thank all multidisciplinary teams in participant centers for their enthusiastic support and following the study interventions.

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