Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA)

ARDS Network

ARDSNet Study 01, Version III

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Ventilator
Roy G. Brower, M.D.
Pulmonary and Critical Care
Johns Hopkins Hospital
720 Rutland Avenue
Baltimore, MD 21205
(410) 955-3468

Eligibility
Gordon R. Bernard, M.D.
Vanderbilt University School of Medicine
1308 Medical Center North
21st Avenue and Garland Street
Nashville, TN 37232
(615) 322-2386

Adverse Events
B. Taylor Thompson, M.D.
Pulmonary and Critical Care
Massachusetts General Hospital
Bulfinch 148
Boston, MA 02114
(617) 724-3705

Data Management
Gail Wenzlow, M.S.W., M.P.H.
ARDS Clinical Coordinating Center
Massachusetts General Hospital-East
149 13th Street, Room 4022
Charlestown, MA 02129
(617)724-9838

Contents

Part I

Study Summary

- **Title:** Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

- **Objectives:** 1) To assess the efficacies of 12 ml/kg vs 6 ml/kg ventilation strategies in reducing mortality and morbidity in patients with acute lung injury and acute respiratory distress syndrome.

- **Study Design:** Multi-Center, prospective, randomized, controlled clinical trial;

  Duration of Study

  1. Enrollment: approximately 24 months.
  2. Study Duration: approximately 30 months.
  3. Patients will be treated for 28 days or until they achieve 48 hours of unassisted breathing.
  4. Patients will be followed for 180 days or until discharged home on unassisted breathing.

- **Sample Size/Interim Monitoring:**

  1. The study will accrue a maximum of 1000 patients.
  2. After every 200 patients the primary efficacy and safety variables will be reviewed by an independent Data and Safety Monitoring Board to determine whether the randomization between 6 and 12 ml/kg ventilation should stop for futility, lack of safety, or proven efficacy. Stopping for futility or efficacy will be based on a formal group sequential stopping boundary.

- **Inclusion Criteria:**

  Acute Onset of:

  1. $PaO_2/FiO_2 \leq 300$ (adjusted for barometric pressure).
  2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph.

3. Requirement for positive pressure ventilation via endotracheal tube.
4. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure $\leq$ 18 mmHg.

- **Exclusion Criteria:**

1. Clinicians caring for patient not agreeable to using Volume Assist/Control ventilation for at least 12 hours.
2. Age $<$ 18 years.
3. Participation in other intervention trials in ALI, ARDS, or sepsis within the past 30 days.
4. $>$ 36 hours since all inclusion criteria are met.
5. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C_5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.
6. Pregnancy (negative pregnancy test for women of child-bearing potential).
7. Increased intracranial pressure, Tricyclic antidepressant overdose (if most recent level elevated or no level), Hgb SS, Hgb SC, or other conditions where hypercapnia would be contraindicated.
8. Severe chronic respiratory disease.
9. Morbid obesity.
10. Burns $\geq$ 30% total body surface area.
11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated $\geq$ 50%.
12. Bone marrow transplant.
13. Lung transplant.
14. Not committed to full support.
15. Severe chronic liver disease (Child-Pugh Score of 10-15).

- **Efficacy:** The two primary efficacy variables are: 1) Percentage of patients alive with unassisted breathing at hospital discharge. Patients still alive in hospital at 180 days will be defined as survivors. 2) Number of Days of Unassisted Breathing, which is defined as the number of days after initiating unassisted breathing to

day 28 after randomization, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. This second primary efficacy measure is related to differences in morbidity and cost attributable to differences in time to recovery from respiratory failure.

Secondary efficacy variables include: 3) Percentage of patients who achieve unassisted breathing, 4) Number of ICU-free days at 28 days after enrollment, 5) Number of Organ-failure-free days at 28 days after enrollment, 6) Number of days meeting commence-weaning criteria at 28 days after enrollment, 7) Number of days after initially achieving unassisted breathing measured at 28 days after enrollment, 8) Incidence of barotrauma (pneumothoraces, pneumatoceles $>$ 2 cm largest diameter, pneumomediastinum), 9) Mortality and days of unassisted breathing for patients with PaO_2/FiO_2 at baseline of less than 200.

PROSPECTIVE, RANDOMIZED, MULTI-CENTER TRIAL OF 12ML/KG VS 6 ML/KG TIDAL VOLUME POSITIVE PRESSURE VENTILATION FOR TREATMENT OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Protocol for the NIH ARDS Network

1 Background

1.1 Ventilatory Strategies

Acute lung injury (ALI) and adult respiratory distress syndrome [1] (ARDS) occur when an event such as sepsis or massive aspiration causes inflammation, increased pulmonary vascular permeability, and extravasation of fluid and inflammatory cells into the pulmonary interstitium and alveolar space ([42]). The inflammatory process leads to inactivation, destruction, and decreased production of surfactant ([15],[40], [45]). This causes increased surface tension at the alveolar air-fluid interface, leading to diffuse microatelectasis. Alveolar flooding and atelectasis cause hypoxemia from shunt. Management of hypoxemic respiratory failure frequently requires positive pressure ventilation. Traditional ventilator management in ALI/ARDS employs positive end-expiratory pressure (PEEP) and generous tidal volumes of $\approx$10-15 ml/kg ([6], [9]). Despite aggressive treatments for the conditions that precipitate ARDS, many patients die without resolution of the lung injury.

Chest x-rays in ALI and ARDS are frequently interpreted as showing diffuse infiltrates. However, CT images, histologic sections, and physiologic studies indicate that the disease is patchy([12] [28]). Much of the ARDS lung is atelectatic or filled with extravascular fluid and is unavailable for ventilation and gas exchange. The remaining lung is relatively normal. When conventional tidal volumes are administered to ALI/ARDS patients, the patent air spaces are distended much more than under conditions of

[1] The recent American-European Consensus Conference on ARDS ([3]) defined ALI according to the following criteria: 1) Acute onset, 2) $PaO_2/FiO_2 \leq 300$, 3) Bilateral infiltrates on frontal chest radiograph, and 4) No evidence of left atrial hypertension (pulmonary capillary wedge pressure $\leq$ 18 when measured). The definition of ARDS was the same except for $PaO_2/FiO_2 \leq 200$.

normal ventilation. The high airway pressures typically observed in ALI/ARDS reflect these high distending forces.

Substantial evidence from animal studies indicates that overdistention of normal lung tissue causes parenchymal inflammation ([56]), increased vascular permeability ([35], [36], [37]), abnormal accumulation of lung water ([56]), alveolar flooding and atelectasis ([10], [23]), radiographic infiltrates([23]), and hypoxemia from shunt ([10], [23]). These findings are very similar to those observed in ALI and ARDS. This suggests that lung injury from overdistention may exacerbate or prevent resolution of ALI and ARDS. Perhaps recovery from respiratory failure and survival from ALI and ARDS would be better using a ventilation strategy that avoided or reduced injurious stretching forces applied to the lung. Recent authoritative sources recommended avoidance of high peak airway pressures to reduce stretch-induced lung injury ([21], [46], [54]). This can be achieved by using smaller tidal volumes and/or lower levels of PEEP. Many intensivists now prescribe smaller positive pressure ventilation tidal volumes in ALI and ARDS. In recent reports, survival was $\approx$80% in >100 severe ARDS patients ventilated with a low tidal volume strategy ([15], [16]). Although there were no concurrent control groups in these reports, survival in comparison to historical experience with ARDS was much improved.

Recently, two prospective, randomized trials of differing ventilator strategies were reported ([1], [48]). Stewart and co-workers studied ~7 ml/kg vs ~ 11 ml/kg tidal volume in 120 patients at high risk for ARDS. They found no difference in mortality, incidence of barotrauma, or organ failures. However, the difference in plateau pressures (22.3 $\pm$ 5 vs. 26.8 $\pm$ 7 cm H_2O for low vs. high tidal volume, respectively) and the sample size were relatively small, precluding a definitive assessment of either the benefit or harm of low tidal volume ventilation ([48], [20]). The study of Amato et al. showed improved survival in a group treated with an "open lung" approach that involved using higher PEEP (adjusted on the basis of an initial pressure-volume curve) and a tidal volume of 6 ml/kg. The comparison group used a tidal volume of 12 ml/kg and PEEP set by traditional oxygenation critieria. This study was also relatively small (53 patients) and the mortality in the control group was unexpectedly high (71%)([1]). It is unclear if the lower mortality in the "open lung" approach patients was due to the limitation of tidal volume, the method of PEEP adjustment, or failures of randomization that caused more high-risk

patients to be assigned to the control group ([20]).

Strategies that reduce lung stretch may entail adverse effects. Ventilation with lower tidal volumes may cause alveolar hypoventilation, hypercapnia, and acidosis. In the previously cited uncontrolled reports([15], [16]), the mean maximum $PaCO_2$ was $\approx$64 mmHg (range 38-158),which was frequently associated with acidosis (mean lowest arterial pH $\approx$7.23, range 6.79-7.45). Respiratory acidosis may diminish cardiac contractility and systemic vascular tone ([24], [47], [50], [55]) However these effects generally occur when adrenergic responses are absent or blocked or when respiratory acidosis is more severe than occurred in the patients treated with low tidal volume ventilation ([15],[16]). In intact dogs and humans ([41]), cardiac output and arterial pressure remained constant or increased with respiratory acidosis. This probably represented predominant sympathetic adrenergic effects. Acidosis may also contribute to dyspnea and agitation in critically ill patients. In animal models of acute lung injury, pulmonary shunt was higher when ventilation was achieved with smaller tidal volumes ([5], [14]). Thus, small tidal volume ventilation may require higher levels of PEEP and FiO_2 to maintain minimally acceptable levels of arterial oxygenation. If lower levels of PEEP are used to reduce lung stretch, higher FiO_2's will be necessary to maintain arterial oxygenation, which could contribute to oxidant-induced lung injury. Support strategies thus often involve trade-offs between gas exchange goals and potential toxicities associated with overdistention and high oxygen concentrations. Clinical data and guidelines to optimize these trade-offs are incomplete.

1.1.1 Preliminary Results

Pilot randomized, controlled clinical trials comparing traditional vs low stretch ventilation strategies in ARDS were completed in Salt Lake City, Utah and in Baltimore, Maryland. Investigators conducting these trials are members of the NIH ARDS Network, and the five hospitals contributing patients represent two of the Network Clinical Center Treatment Groups. The experience gained from these ongoing trials, as well as the cumulative experience of Network members in other studies in ARDS ([2], [4], [19], [29], [31], [32], [38], [39], [43], [44], [49], [51]) and sepsis ([3], [11], [13], [22], [59]) provide the basis for the proposed Network multicenter trial.

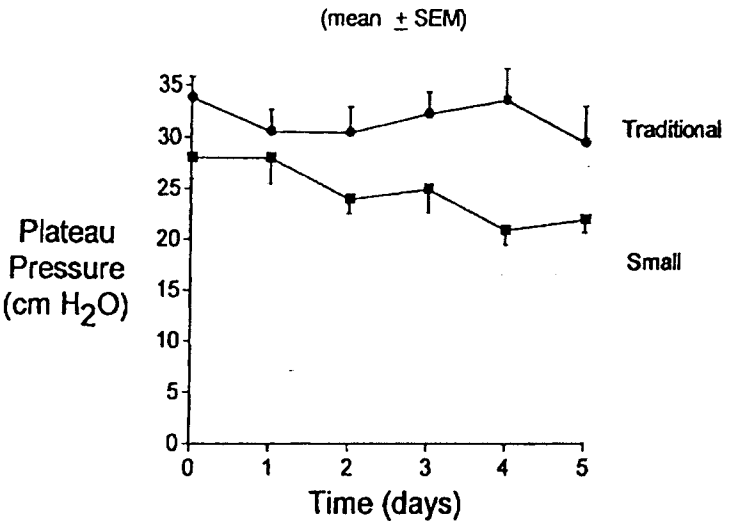
In both pilot trials, ARDS was defined as: $PaO_2/FiO_2 \leq 200$, diffuse infiltrates on frontal chest radiograph, and no evidence of heart failure/fluid overload. Patients were excluded from both trials for pregnancy, conditions that would contraindicate hypercapnia (such as intracranial hypertension), and comorbid conditions where survival would be very unlikely (such as metastatic cancer unresponsive to treatment).

Baltimore

From May, 1994 through March, 1996, 52 patients were enrolled in 8 intensive care units at four hospitals in Baltimore. In this trial, patients were enrolled within 24 hours of when the last inclusion criterion was met, resulting in either traditional or low stretch ventilation at relatively early phases of ARDS. All patients received volume-cycled ventilation in either the Assist/Control or Synchronized IMV modes. Ventilator rate was adjusted up to a maximum of 30/min in both groups to achieve arterial PCO_2 = 30-45, if possible. Patients assigned to traditional ventilation received initial tidal volume = 10-12 ml/kg ideal body weight (IBW). This was adjusted only if necessary to maintain end-inspiratory alveolar (plateau) pressure $\leq$ 50 cmH_2O. Patients assigned to low stretch ventilation received initial tidal volume = 8 ml/kg IBW. This was subsequently reduced by 0.5 ml/kg until the plateau pressure $\leq$ 30. In both traditional and low stretch groups, inspiratory flow rate and pattern were adjusted to maintain I:E ratio $\leq$ 1:1. In both groups, oxygenation goals were the same: $55 \leq PaO_2 \leq 75$ or $86\% \leq SpO_2 \leq 95\%$. Moreover, oxygenation was maintained in the target ranges using the same sequence of $PEEP/FiO_2$ combinations (e.g. 7.5/.50, 10/.50, 10/.60,....). In both groups, bicarbonate was allowed if arterial pH < 7.30 and was required if pH < 7.20.

The following data were available after the first 34 patients completed the protocol (either death or unassisted ventilation for 48 hours). Fifteen patients were randomized to receive the traditional treatment; 19 received the low stretch treatment. Since the incidence of death or extubation became substantial after 5 days, physiologic variables were analyzed for only this initial period. The mean plateau pressures were maintained below the target of 30 cmH_2O in the low stretch group (Figure 1). In the traditional treatment group, plateau pressures were highly variable, with mean plateau pressures $\approx$ 33 cm H_2O.

Figure 1: Plateau Pressure vs Time



For many traditional treatment patients, it was necessary to reduce tidal volumes at entry to achieve the protocol tidal volume of 10-12 ml/kg IBW. On average, the "traditional" tidal volume of 10-12 ml/kg IBW was a conservative estimate of those in common use. In many low-stretch patients, there was little or no hypercapnia in the first 5 days after tidal volume reduction (Figure 2); only 3 of the 19 patients experienced elevations in $PaCO_2$ to > 60 mmHg during the initial 5 days. Effects on acid-base balance were also relatively mild (Figure 3).

The relatively small separation in mean plateau pressures (Figure 1) between groups was partially due to the conservative tidal volumes in many "traditional" patients and the relatively mild initial tidal volume reductions in the low stretch patients. In the proposed protocol, patients assigned to the traditional treatment group will receive initial tidal volume = 12 ml/kg IBW, which will be more representative of "traditional" treatment. Patients assigned to the low stretch treatment will receive initial tidal volume = 6 ml/kg IBW, which will result in lower plateau pressures.

The process of weaning patients from mechanical ventilation was not controlled in this trial. Decisions regarding commencement of weaning and

Figure 2: $PaCO_2$ vs Time

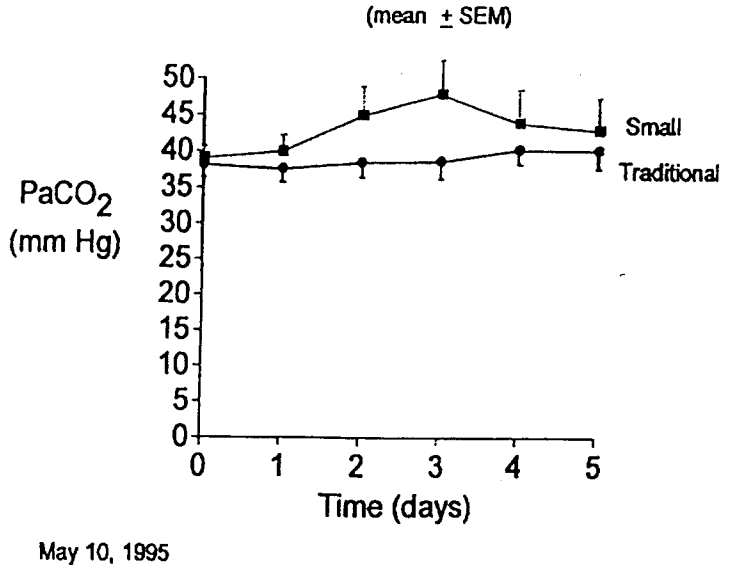
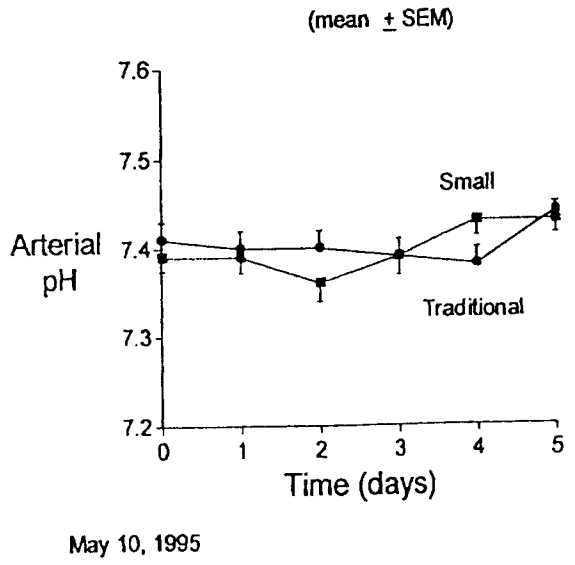


Figure 3: Arterial pH vs Time



weaning technique were made by the clinicians caring for individual patients. Most survivors were weaned with either progressive reductions in Pressure Support or SIMV frequency, or some combination of Pressure Support and SIMV.

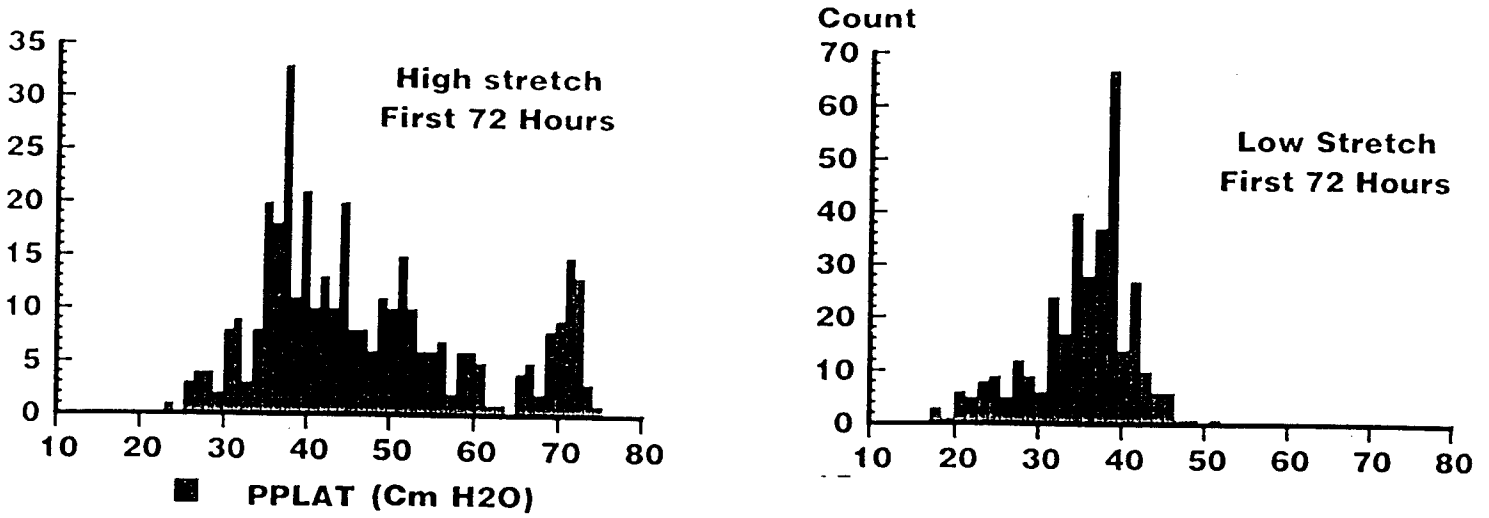
Salt Lake City

The trial in Salt Lake City was conducted with computerized point-of-care systems that provided decision support tools and data acquisition. Many patients were referred to the LDS Hospital from the surrounding communities and region. Most patients were enrolled within several days of the onset of ARDS, but patients may be enrolled up to 21 days after the entry criteria were met. Therefore, this trial includes some patients in the late as well as early phases of ARDS. Between May, 1994 and May, 1995, 38 patients were enrolled in this trial.

All patients received volume cycled ventilation in the Assist/Control mode. Ventilator rate, I:E ratio, inspiratory flow pattern, and oxygenation were managed according to the same rules in both groups. Low stretch patients received initial tidal volume = 6 ml/kg. This was adjusted to 5 and then 4 ml/kg if necessary to maintain plateau pressure $\leq$ 35 cmH_2O. High stretch patients received initial tidal volume = 10 ml/kg, which was increased up to 15 ml/kg if necessary to achieve plateau pressure $\geq$ 45 cmH_2O. This protocol achieves greater separation of plateau pressures between treatment groups (figure 4).

Weaning was rigorously controlled in this trial to prevent potential systematic differences in weaning approaches between groups. Weaning by daily CPAP trials commenced when PEEP $\leq$ 12 cmH_2O and $FiO_2 \leq 0.5$. Each trial continued to sustained unassisted ventilation unless respiratory rate, tidal volume, or oxygenation deteriorated to specific thresholds. The proposed Network protocol will also rigorously control weaning. Many of the same rules that govern commencement and continuation of weaning are incorporated in the proposed trial. This will help to minimize between-group variability in ventilator days due to inadvertent systematic biases in weaning approaches.

Figure 4: Frequency of Plateau Pressures by Treatment Group



2 Objectives

The proposed study is designed to compare the efficacies of two ventilation strategies in reducing mortality and morbidity in ALI and ARDS. The two different strategies incorporate different prioritizations of clinical variables. The 12 ml/kg approach to ventilation in ALI and ARDS aims to preserve acid-base balance and utilize lower FiO_2's, even if it requires ventilating with high airway pressures that may contribute to acute lung injury. The 6 ml/kg strategy aims to reduce lung overdistention, even if it requires tolerating worse gas exchange and acid-base balance.

3 Study Design

This is a randomized, controlled multi-center study. Patients will be recruited from ICUs in approximately 24 hospitals that comprise the NIH ARDS Network. Each candidate will be evaluated for eligibility by the principal investigator of the ARDS Network Center or a designee. Following enrollment, each patient will be classified into strata according

to hospital. Within each stratum, patients will be randomized to either the 12 ml/kg ventilation or 6 ml/kg ventilation treatment group.

End-Points

There will be two primary efficacy measures: 1) *Percentage of patients alive with unassisted breathing at hospital discharge.* Patients still alive in hospital at 180 days will be defined as survivors. This efficacy measure is used to calculate sample size and to develop interim stopping boundaries. Since survival may be affected by many factors that are indirectly or remotely related to recovery from ARDS or ALI, the following second primary efficacy measure is designed to examine differences in time to recovery from respiratory failure. This will also reflect morbidity and cost. 2) *Number of Days of Unassisted Breathing*, which is defined as the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. For example, if a patient begins unassisted breathing on day 16 and survives to day 28, he/she will be assigned a value of 12. If a similar patient begins unassisted breathing on day 16 but dies on day 25, he/she will be assigned a value of 9. If a patient survives for $>$ 48 consecutive hours of unassisted breathing but requires assisted breathing (for any reason) before day 28, he/she will be assigned only the number of days of unassisted breathing before day 28. Patients who die without initiating unassisted breathing or before 48 consecutive hours of unassisted breathing will be assigned a value of zero. Patients transferred to another hospital or other health care facility (intermediate care, nursing home etc.) while still on positive pressure ventilation will be followed to assess these primary efficacy measures.

Number of Days of Unassisted Breathing is related to "number of days of assisted ventilation", which would be a simpler measure. However, if there were a trend in one treatment group towards more rapid death on assisted ventilation, the effect of this trend on duration of assisted ventilation would be misleading. "Average duration of ventilation in survivors" would avoid this potential problem. However, if there were a trend towards better survival in one treatment group even though the days of assisted ventilation were longer in the survivors, then the measure of days of assisted ventilation in survivors would be of questionable value. The second primary efficacy measure chosen for this study, *Number of Days of Unassisted Breathing*, will be favorably affected by both better survival

and shorter duration of ventilation in survivors.

Secondary endpoints include:

3. Percentage of patients who achieve unassisted breathing.
4. Number of ICU-free days at 28 days after enrollment.
5. Number of Organ-failure-free days at 28 days after enrollment.
6. Number of days after first meeting commence-weaning criteria, measured at 28 days after enrollment.
7. Number of days after initially achieving unassisted ventilation, measured at 28 days after enrollment.
8. Incidence of barotrauma (pneumothoraces, pneumatoceles > 2 cm largest diameter, pneumomediastinum).
9. Mortality and days of unassisted breathing for patients with PaO_2/FiO_2 at baseline of less than 200.

4 Study Population and Enrollment

4.1 Number/Source/Screening

The trial will accrue a maximum of 1000 patients in two years. Patients with either ALI or ARDS will be recruited from intensive care units (ICU's) in approximately 24 hospitals that comprise the NIH ARDS Network. Each of the ten Centers that comprise the ARDS Network have provided documentation of at least 100 ARDS patients per year and of the potential to enroll approximately 40 patients per year in multicenter studies in ARDS and sepsis.

Study Coordinators at each site will visit each intensive care unit daily to identify potential candidates for enrollment (see inclusion criteria, section 4.2 and exclusion criteria, section 4.3). Permission to approach patients/families will be requested from attending physicians. All patients meeting the study inclusion criteria (section 4.2) will be entered on a screening log. The screening log will include information explaining why

patients meeting the inclusion criteria are not enrolled (exclusion criteria, attending physician denial, patient refusal, etc.).

4.2 Inclusion Criteria

Acute Onset of:

1. $PaO_2/FiO_2 \leq 300$. If altitude > 1000m, then $PaO_2/FiO_2 \leq 300$ x (B.P./760).
2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.
3. Requirement for positive pressure ventilation via endotracheal tube.
4. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure $\leq$ 18 mmHg.

Criteria 1-3 must occur together within a 24-hour interval.

The term 'acute onset' is defined as follows: the hypoxia criterion (#1) and the chest radiograph criterion (#2) must be in effect for $\leq$ 28 days at the time of randomization.

4.3 Exclusion Criteria

1. Clinicians caring for patient not agreeable to using Assist/Control Ventilation for at least 12 Hours after patient enrollment. (This exclusion criterion is intended to avoid enrollment of patients who may begin weaning within 12 hours. It is *not* implied that other forms of ventilation or gas exchange support, such as pressure control ventilation or ECMO, are allowed in this study after 12 hours.)
2. Age < 18 years.
3. Participation in other intervention trials in ALI, ARDS, or sepsis within the past 30 days.

4. > 36 hours since all inclusion criteria are met (see "Enrollment Time Window", Section 4.4).

5. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C_5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.

6. Pregnancy (negative pregnancy test for women of child-bearing potential).

7. Elevated intracranial pressure (Appendix A), Tricyclic antidepressant overdose (if most recent level elevated or no level), Hgb SS, Hgb SC, or conditions in which hypercapnia would be contraindicated.

8. Severe chronic respiratory disease (eg COPD, pulmonary fibrosis, morbid obesity, and other chronic diseases of the lung, chest wall or neuromuscular system. (Appendix A).

9. Morbid obesity (> 1 kg/cm body weight).

10. Burns $\geq$ 30% total body surface area.

11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated $\geq$ 50%.

12. Bone marrow transplant.

13. Lung transplant.

14. Not committed to full support (Exception: A patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).

15. Severe chronic liver disease (Child-Pugh Score of 10-15(Appendix A)).

4.4 Enrollment and Study Initiation Time Window

All patients must be enrolled, randomized, and initial ventilator adjustments made within 36 hours of the time the last inclusion criterion was met. The last inclusion criterion may be met at either the network

hospital or a referring hospital. The 36-hour window for enrollment will begin at the time of documentation of the last inclusion criterion, regardless of location. Initial ventilator changes must occur within 4 hours of the time of randomization, and must be made within 36 hours of the time that the last inclusion criterion was met.

4.5 Informed Consent

Informed consent will be obtained from each patient or surrogate.

4.6 Randomization

After procuring a signed and dated informed consent, the data coordinating center will be called and an assignment will be made by computer-generated randomizations to either the 12 ml/kg or 6 ml/kg group. Randomization is by permuted blocks by hospital. There are ten clinical centers but each may have more than one hospital participating.

Randomization system will be based on Interactive Voice Response technology. Each research coordinator will have a unique Personal Identification Number (PIN). She or he will call the system and be asked to supply the PIN. A ventilator strategy, either 12 ml/kg or 6 ml/kg, and a patient ID number will be assigned.

4.7 Minorities/Women

Gender and racial patient subsets were considered by the NHLBI in selecting the Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate patient population contains representative proportions of minorities (28%) and women. Recruitment of minorities and women will be monitored by the Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

Randomization will result in approximately equal numbers of patients

assigned to the treatment arms within each population subset. It will be possible to make statistical comparisons within these subsets; however, any inferences derived from these analyses will be of low power because of the relatively small number of patients within the subsets. The primary value of such analyses would be for generating additional hypotheses, which is appropriate given the current lack of evidence of gender or race-related interactions with either of the two treatment interventions in the proposed study.

5 Study Procedures

5.1 Ventilator Procedures

5.1.1 Volume Cycled Ventilation

1. Ventilator mode.

   12 ml/kg and 6 ml/kg Treatment Groups: Volume Cycled Assist Control.

2. Tidal Volume and Ventilator Rate Adjustments and Arterial pH Management.

   (a) Initial Ventilator Tidal Volume and Rate.

   Tidal Volume

   (In the following procedures, the term "tidal volume " refers to inspired volumes, corrected for gas compression in the ventilator conduits.)

   12 ml/kg group: 12 ml/kg ideal body weight (IBW). [2]

   6 ml/kg group: 6 ml/kg IBW. Initial tidal volumes in this group will be set at 8 ml/kg IBW. This will be reduced by 1 ml/kg IBW at intervals of $\leq$ 2 hours until tidal volume = 6 ml/kg IBW.

[2]Ideal weight is calculated from age, gender and height (heel to crown) according to the following equations:
Males: IBW (kg) = 50 + 2.3 (height (inches) - 60).
Females: IBW (kg) = 45.5 + 2.3 (height (inches) - 60).

Ventilator Rate

Both groups: Initial ventilator rate will be set to match minute ventilation prior to enrollment, if possible. Maximum rate = 35/min.

(b) Adjustments to Ventilator Tidal Volume and Rate.

Goals: Ventilator rate and tidal volume will be adjusted to achieve specific goals of arterial pH and end-inspiratory alveolar (plateau) pressure, respectively.

- **Arterial pH Goals**

  Goal for both groups: $7.30 \leq \text{pH} \leq 7.45$.

  Arterial pH will be measured when clinically indicated. Management of alkalemia and acidemia may be according to the following rules:

  - Alkalemia (pH > 7.45): Decrease ventilator rate, if possible.
  - Mild acidemia ($7.15 \leq \text{pH} < 7.30$):
    i. Increase ventilator rate up to maximum of 35 or until pH > 7.30 or $PaCO_2 < 25$ mm Hg.
    ii. If ventilator rate = 35 or $PaCO_2 < 25$, then bicarbonate infusion may be given.
  - Severe acidemia (pH < 7.15):
    i. Increase ventilator rate to 35.
    ii. If ventilator rate = 35 and pH < 7.15 and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until $\text{pH} \geq 7.15$ (under these conditions, the plateau pressure targets described below may be exceeded).

- **Plateau Pressure Goals**

  12 ml/kg group: ≤ 50 cm H_2O

  6 ml/kg group: ≤ 30 cm H_2O

  Plateau pressures will be measured at a minimum frequency of q4 hours. Plateau pressures will also be measured and recorded 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients will be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause

will be recorded. The pause will be removed for at least 6 breaths. The plateau pressure measurements will be replicated 3 times with at least 6 "non-plateau" breaths between measurements and the mean of the three values will be calculated. If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressure will be substituted.

Tidal volumes will be reduced (if arterial pH > 7.15, see section 2b above) by 1 ml/kg q2-3 hours if necessary to maintain plateau pressures $\leq$ the respective target values.

The minimum tidal volume in both groups will be 4 ml/kg IBW.

Changes in the tidal volume, if indicated above, will be made within five minutes.

Tidal volumes will be increased in both groups if plateau pressure << targets:

i. 12 ml/kg group: if tidal volume < 12 ml/kg and plateau pressure $\leq$ 45 cm H_2O, then tidal volume will be increased in steps of 1 ml/kg until plateau pressure $\geq$ 45 or tidal volume = 12 ml/kg IBW.

ii. 6 ml/kg group: if tidal volume < 6 ml/kg and plateau pressure $\leq$ 25 cm H_2O, then tidal volume will be increased by 1 ml/kg until plateau pressure $\geq$ 25 or tidal volume = 6 ml/kg IBW.

iii. If tidal volume < 8 ml/kg AND Pplat < 30 cm H_2O AND airway pressure remains below the PEEP level during inspiration or the ventilator delivers frequent ($\geq$ 3/minute) double breaths because airway pressure falls below trigger threshold at the end of inspiration, then tidal volume will be increased by 1 ml/kg. If these phenomena persist at tidal volume = 8 ml/kg or with Pplat $\geq$ 30 cm H_2O, then additional sedation or neuromuscular blockade should be considered.

3. Inspiratory flow and I:E ratio.

Inspiratory flow rate will be adjusted to maintain the I:E ratio = 1:1.0–1:3.0.

4. Oxygenation.

In both treatment groups, the target ranges for oxygenation will be:

$$\mathbf{55\ mmHg \leq PaO_2 \leq 80\ mm\ Hg}$$
or
$$\mathbf{88\% \leq S_pO_2\text{ - sat} \leq 95\%}$$

When both PaO_2 and S_pO_2 are available simultaneously, the PaO_2 criterion will take precedence.

Oxygenation will be maintained in the target ranges using the following PEEP/FiO_2 combinations: (see table below)

FiO_2	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20–24

Levels of PEEP in this scale represent levels set on the ventilator, not levels of total PEEP, auto-PEEP, or intrinsic PEEP.

Arterial oxygenation will be assessed by either SpO_2 or PaO_2 at a minimum frequency of q4 hours. When SpO_2 is used to assess arterial oxygenation, the following measures will be taken if possible to improve accuracy: the SpO_2 sensor will be checked to ensure optimal position, cleanliness, and consistent readings with satisfactory waveforms; no position changes or endobronchial suctioning for $\geq$ 10 minutes; no invasive procedures or ventilator changes for $\geq$ 30 minutes. SpO_2 will be observed for a minimum of 1 minute, and a representative value will be recorded on the appropriate source-document flowsheet.

If arterial oxygenation is not within the target range, then FiO_2 or PEEP will be adjusted within 30 minutes. Following these adjustments, oxygenation will be reassessed within 15 minutes and subsequent adjustments made if necessary.

If a patient's PEEP/FiO_2 is not compatible with the PEEP/FiO_2 scale (e.g. immediately after enrollment or after urgent changes in FiO_2 or PEEP in response to desaturations, hypotension, etc.), either PEEP or FiO_2 (or both) will be adjusted at intervals of 5-15 minutes until the PEEP/FiO_2 is compatible with the scale. The

procedures for adjusting PEEP and FiO_2 to make them compatible with the scale are outlined in Appendix D.

In the 6 ml/kg treatment group, if $PaO_2 < 55$ mm Hg or $SpO_2 < 88\%$ and tidal volume = 4 ml/kg IBW (or the minimum tidal volume necessary for pH control, section 2 above) and plateau pressure ≥ 30, then FiO_2 will be raised until $PaO_2 \geq 55$ or $SpO_2 \geq 88\%$ or $FiO_2 = 1.0$. If $PaO_2 < 55$ mm Hg or $SpO_2 < 88\%$ and $FiO_2 = 1.0$, PEEP will be raised by 2 cm H_2O increments to 24 cm H_2O.(In these circumstances, plateau pressure may exceed 30 cm H_2O).

In the 12 ml/kg treatment group, if $PaO_2 < 55$ mm Hg or $SpO_2 < 88\%$ and tidal volume = 4 ml/kg IBW (or the minimum tidal volume necessary for pH control, section 2 above) and plateau pressure ≥ 50, FiO_2 will be raised in increments of 0.1 until $PaO_2 \geq 55$ or $SpO_2 \geq 88\%$ or $FiO_2 = 1.0$. If $PaO_2 < 55$ or $SpO_2 < 88\%$ and FiO_2 1.0, then PEEP will be raised by 2 cm H_2O increments to 24 cmH_2O.(In these circumstances, plateau pressure may exceed 50 cm H_2O).

Brief periods (≤ 5 minutes) of $S_pO_2 < 88\%$ or $> 95\%$ may be tolerated without making changes in PEEP or FiO_2.

$FiO_2 = 1.0$ may be used for brief intervals (≤ 10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

If $FiO_2 = 1.0$ and PEEP = 25 cm H_2O and I:E = 1.0 and $PaO_2 < 55$ or $SpO_2 < 88\%$, then a PEEP increase trial *may* be performed as follows:

(a) Increase PEEP by 2-5 cm H_2O increments to a maximum of 34 cm H_2O or until $PaO_2 \geq 55$ or $SpO_2 \geq 88\%$.

(b) If the PEEP increase trial is not effective within four hours (PaO_2 increased by at least 5 mmHg), then PEEP will be returned to 24cm H_2O.

5. Simultaneous changes

Changes in more than one ventilator setting driven by measurements of PO_2, pH, and plateau pressure may be performed simultaneously, if necessary. Arterial blood gases will be obtained after all ventilator changes as clinically indicated.

5.1.2 Weaning

1. Commencement of Weaning.

   Patients will be assessed for the following criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to four hours.

   (a) $\geq$ 12 hours since initial protocol ventilator changes, if any.

   (b) $FiO_2 \leq .40$.

   (c) Values of both PEEP and $FiO_2 \leq$ values from previous day (comparing Reference Measurement values, section 6.3).

   (d) Not receiving neuromuscular blocking agents and without neuromuscular blockade.

   (e) Patient exhibiting inspiratory efforts. Ventilator rate will be decreased to 50 % of baseline level for up to 5 minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.

   (f) Systolic arterial pressure $\geq$ 90 mm Hg without vasopressor support ($\leq$ 5 μg/kg/min dopamine or dobutamine or equivalent low dose of another vasopressor will not be considered a vasopressor).

   If criteria a-f are met, weaning potential will be assessed during a CPAP trial of $\leq$ 5 minutes at CPAP = 5 cm H_2O and FiO_2 = .50. If respiratory rate remains $\leq$ 35/min during the 5-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the Pressure Support Wean Procedure (Section 2). If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the patient will resume A/C ventilation at the most recent settings. The patient will be reassessed for weaning the following day at 0600-1000. (If failure to maintain the respiratory rate $\leq$ 35 during the CPAP trial is attributed primarily to anxiety, then appropriate treatment for anxiety will be given and a second 5-minute CPAP trial initiated within 4 hours).

2. Initial Pressure Support (PS) Setting (for patients whose respiratory rates remain $\leq$ 35/min during 5-minute CPAP trial).

   (a) Mode = Pressure Support. Only the following PS levels may be used: 5, 10, 15, and 20 cm H_2O.

   (b) If respiratory rate $\leq$ 25 during the 5-minute CPAP trial and tolerance criteria (section 3, below) are met then initiate PS = 5 cm H_2O.

   If respiratory rate = 26-35 during the 5-minute CPAP trial then set initial PS = 20 cm H_2O and make adjustments in PS within 5 minutes if necessary to achieve respiratory rate = 26-35.

   (c) PEEP = 5 cm H_2O.

   (d) FiO_2 = .50.

3. Assessment for Tolerance.

   Patients will be assessed for tolerance using the following criteria:

   (a) Total respiratory rate < 35 ($\leq$ 5 min at respiratory rate > 35 may be tolerated).

   (b) $SpO_2 \geq$ 88% (< 15 min at < 88% may be tolerated).

   (c) No respiratory distress (two or more of the following):

      i. Heart rate greater than 120% of the 0600 rate($\leq$ 5 min at > 120% may be tolerated).

      ii. Marked use of accessory muscles.

      iii. Abdominal paradox.

      iv. Diaphoresis.

      v. Marked subjective dyspnea.

   If any of goals a,b, or c are not met on initial set-up to PS, then the ventilator mode will be changed back to A/C at back-up rate = to most recent A/C settings and the patient will be reassessed the next morning.

4. Subsequent Ventilator Settings.

   (a) Reduce PS level by 5 cm H_2O q1-3 hours. PS will not be decreased below 5 cm H_2O. No decreases in PS will be made after 1900.

(b) If PS = 10, 15 or 20 cm H_2O is not tolerated, then return to A/C (patient will remain in previously assigned 12 ml/kg or 6 ml/kg treatment group).

i. At 0600-1000 of the next day, return to last PS level tolerated and continue with step 4(a).

(c) If PS level = 5 cm H_2O is not tolerated, increase PS by 5 cm H_2O to 10 cm H_2O, and maintain until the following morning.

i. If a patient on PS = 5 or 10 must go back to A/C for reasons other than intolerance to weaning (e.g. surgical or other invasive procedures), the weaning sequence will be re-entered with section 5.1.2.1.

(d) If PS = 5 cm H_2O is tolerated for two or more hours (using tolerance criteria 3a-c above), assess for ability to sustain unassisted breathing (section 5 below).

5. Assess for Ability to Sustain Unassisted Breathing.

Initiate a trial of spontaneous breathing on CPAP $\leq$ 5 cm H_2O, T-piece, or tracheostomy mask with $FiO_2 \leq .50$. Monitor for the following:

(a) $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mmHg.

(b) Spontaneous tidal volume $\geq$ 4 ml/kg ideal body weight.

(c) Respiratory Rate $\leq$ 35/min.

(d) pH $\geq$ 7.30 if measured.

(e) No respiratory distress (2 or more of the following):

i. Heart rate > 120% of the 0600 rate ($\leq$ 5 min at > 120% may be tolerated).

ii. Marked use of accessory muscles.

iii. Abdominal paradox.

iv. Diaphoresis.

v. Marked subjective dyspnea.

If criteria a-e are met for > 120 minutes, continue with unassisted breathing (step 6). If any of criteria a-d are not met during the 120 minute trial, then resume PS ventilation at 5 cm H_2O and assess for tolerance (step 3).

6. Definition of Unassisted Breathing.

(a) Extubated with face mask, nasal prong oxygen, or room air, OR

(b) T-tube breathing, OR

(c) Tracheostomy mask breathing, OR

(d) CPAP $\leq$ 5 without PS or IMV assistance.

5.1.3 Completion of Ventilator Procedures

Patients will be considered to have completed the study ventilator procedures if any of the following conditions occur:

1. Death.
2. Hospital discharge.
3. Alive 28 days after enrollment.

If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures will resume unless the patient was discharged from the hospital or > 28 days elapsed since enrollment.

5.1.4 Premature Withdrawal from Treatment

Patients will be removed from the 6 ml/kg tidal volume ventilation protocol if they develop neurologic conditions where hypercapnia would be contraindicated (Appendix A.7).

6 Data Collection

6.1 Background Assessments

1. Demographic and Admission Data.
2. Pertinent Medical History and Physical Examination.

3. Height; calculated ideal body weight (IBW).

4. Time on Ventilator prior to enrollment.

5. Type of Admission

   (a) Scheduled surgical

   (b) Medical

   (c) Unscheduled surgical

6. Presence of following chronic diseases:

   (a) Metastatic cancer (proven by surgery, computed tomographic scan, or other documented method.

   (b) Hematologic malignancy (lymphoma, acute leukemia, or multiple myeloma).

   (c) AIDS with complications (PCP pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasmosis).

6.2 Baseline Assessments

The following information will be recorded during the four-hour interval that precedes initial protocol ventilator changes (if any). Parameters indicated with "* " will be measured during the four-hour interval. If more than one value is available during the four-hour interval, the last value will be recorded. For other parameters, most recent values will be recorded. If no values are available during the preceding 24 hours, then values will be measured during the four-hour interval prior to initial ventilator changes (if any).

1. * Vital Signs: heart rate (b/min), systolic and diastolic BP (mmHg), body temperature (°C) , total respiratory rate.

2. * Ventilator Parameters: Mode, ventilator rate, tidal volume (inspired), FiO_2, PEEP, plateau pressure (0.5 second pause), ventilator manufacturer and model.

3. Body weight (kg).

4. Arterial PO_2, PCO_2, and pH and SpO_2.
5. Urinary output (most recent 24 hour value).
6. Serum electrolytes, BUN, creatinine and glucose.
7. Blood hematocrit/hemoglobin, WBC , and platelets.
8. Serum albumin concentration.
9. * Blood for drug levels, cytokines and mediators. Blood will be drawn sufficient to yield 6 ml of EDTA anticoagulated plasma and divided immediately after centrifugation into 3 equal 2 ml aliquots in specified tubes and frozen at -70°C.
10. * Glasgow coma score
11. Frontal chest radiograph (when available):
    (a) Radiographic Lung Injury Score ([33], # of quadrants.
    (b) Presence/absence of barotrauma:
        i. pneumothoraces (R/L)
        ii. pneumomediastinum
        iii. pneumatoceles > 2 cm minimum diameter (R/L)
        iv. subcutaneous emphysema
12. Administration of the following medications (Y/N):
    (a) Sedatives
    (b) Neuromuscular blocking agents
    (c) Vasopressors (maximum number given simultaneously)

Most recent values for the following additional parameters will be recorded only if they are available from clinically required measurements.

13. Pulmonary artery systolic, diastolic, mean and pulmonary capillary wedge pressures, central venous pressure, and cardiac index.

6.3 Assessments During Enrollment

The following data will provide the basis for assessing protocol compliance and safety as well as between-group differences in several efficacy variables. Data for each of the variables will be recorded on the days shown in the Time-Events schedule (Appendix C) or until death, discharge from intensive care unit, or unassisted ventilation for 48 hours.

Reference Measurements

The following parameters will be measured and recorded between 0600 and 1000 on the days specified in the Time-Events schedule (Appendix C). The following conditions will be ensured prior to measurements: supine position for $\geq$ 15 minutes; no endobronchial suctioning for $\geq$ 10 minutes; no invasive procedures or ventilator changes for $\geq$ 30 minutes. SpO_2 sensors will be checked for optimal position, cleanliness, and consistent readings with satisfactory waveforms, if displayed. SpO_2 values will be observed for 1 minute and a representative value recorded. All vascular pressures will be zero-referenced to the mid-axillary line.

1. If receiving positive pressure ventilation:
   (a) Ventilator mode
   (b) Ventilator set inspired tidal volume (if on volume cycled mode)
   (c) Pressure Support level (if on PS for weaning)
   (d) Total respiratory rate
   (e) Total minute ventilation
   (f) PEEP
   (g) Plateau pressure (if on volume cycled mode)
   (h) Peak inspiratory pressure (if on volume cycled mode)
2. FiO_2
3. SpO_2 on current FiO_2
4. Hemodynamic values
   (a) Arterial systolic, diastolic and mean pressures

(b) Heart Rate (beats/min)

Values for the following variables will be recorded
for the dates shown in the Time-Events Schedule.
If the measurements are not obtained during the 4-hour reference interval, then the single value obtained closest in time to the reference interval on the respective date will be recorded.
If more than one value is obtained during the reference interval, then the earliest value during the interval will be recorded.

5. Weight (kg), using same technique for each measurement (bed-scale vs lift vs other)

6. Blood hemoglobin concentration

7. Arterial PO_2, PCO_2, and pH and calculated bicarbonate concentrations

8. Requirements for the following medications (Y/N):

   (a) Sedatives and tranquilizers

   (b) Neuromuscular blocking agents

   (c) Vasopressors (maximum number given simultaneously)

   (d) Experimental treatments: nitric oxide, fluorocarbons, surfactants, extracorporeal gas exchange (ECMO, $ECCO_2R$, etc.)

9. AP frontal chest radiograph
   Presence/absence of barotrauma (as described for baseline assessments)
   Radiographic Lung Injury Score ([33], number of quadrants)

10. Brussels Score

    (a) Worst PaO_2/FiO_2 ratio for the date

    (b) Worst systolic blood pressure for the date

    (c) Worst creatinine, bilirubin, and platelet count for the date

    (d) Use of a vasopressor (Y/N)

    (e) Glasgow Coma Score

6.3.1 Ventilator protocol monitoring

Ventilator parameters, pH, and SpO_2 will be recorded daily at randomly selected times to assess for accuracy of the ventilator settings relative to the protocol requirements. The following parameters will be recorded:

1. Ventilator mode
2. Tidal volume
3. Respiratory rate (set)
4. Plateau pressure
5. I:E ratio
6. FiO_2
7. PEEP
8. Corresponding pH and SpO_2, when available.

6.4 Endpoint determinations

1. Patient vital status at discharge or 180 days after enrollment.
2. Time of initiation of unassisted breathing.
3. Patient status 48 hours after initiation of unassisted breathing.
4. Date of ICU discharge.
5. Date of hospital discharge.

7 Statistical Considerations

This study is a 2×2 factorial design comparing 6 ml/kg tidal volume to 12 ml/kg tidal volume Volume Assist/Control ventilation and comparing lisofylline injection to placebo. The ventilator and the lisofylline trials will be analyzed separately and one may stop before the other.

There are two primary efficacy measures. The first is *Percentage of patients alive with unassisted breathing at hospital discharge.* Patients still alive in hospital at 180 days will be defined as survivors. For the analysis, survival of the two groups will be compared using a test based on the 180-day Kaplan-Meier estimate. This efficacy measure is used to calculate sample size and to develop interim stopping boundaries. The second efficacy measure, *Number of Days of Unassisted Breathing*, is designed to examine differences in time to recovery from acute respiratory failure, which will reflect morbidity and cost (see Section 3, Study Design). *Number of Days of Unassisted Breathing* will be compared between treatments using a Wilcoxon test.

7.1 Treatment of multiple endpoints

We do not plan to use a bonferroni correction to correct for the fact that there are two efficacy measures because these measures are affected by different effects of treatment. If a treatment does not reduce mortality it may still reduce the duration of mechanical ventilation which would benefit patients financially and decrease their morbidity. This effect is measured by *Number of Days of Unassisted Breathing.* This is a better efficacy measure than the duration of ventilation for all patients or the duration of ventilation for survivors because, in either case, the duration of ventilation is potentially biased against a treatment that saves the lives of a portion of the patients by increasing the time that they must be ventilated.

7.2 Sample size and early stopping for the ventilator protocol

7.2.1 Sample size

The sample size depends on the magnitude of the difference in mortality that is considered important. The study is designed to detect a difference between 6 ml/kg tidal volume and 12 ml/kg tidal volume of 10%, from 40% to 50%.

7.2.2 Early stopping

There will be four interim analyses and one final analysis at 200, 400, 600, 800, and 1000 patients. The interim analyses will use the sequential design described in DeMets and Ware ([8] pp 661-3.Table 1, $N = 5, 1 - \beta = .9, \alpha = .025$). With this design we achieve an 87% power to show a 10% difference in mortality rate (From 40% to 50%) at a two-sided significance level. The cumulative probabilities of rejecting a true null hypothesis for this design are $\alpha_i, i = 1, \ldots, 5 = 3.1 \times 10^{-6}, 7 \times 10^{-4}, .0048, .01335, .025$ at the 5 interim analyses and the z-scores to stop and declare superiority at 200, 400, 600, 800, and 1000 patients are 4.5213296, 3.1970628, 2.6103909, 2.2606648, 2.0220001. The z-scores to stop for futility are -0.7740587, -0.0184263, 0.4168130, 0.7349707, 0.9918935. .1 100 2.277 1.496 2.022".

The analysis plan for mortality is based on the last value of the Kaplan-Meier curve which will always occur on or before 180 days. Patients who leave the hospital alive, off the ventilator are assumed to be alive at 180 days.

The z-score used for each analysis will be calculated using a stratified analysis where differences between ventilator strategies calculated within each strata are weighted by the inverse of their variance and summed. The strata are defined by concurrent randomized drug treatment.

At each analysis the information available may differ from the amount of information provided by 200, 400, 600, or 800 patients. The *effective sample size* at the ith analysis will be calculated as the sample size that would give the observed variance if all information were available. The stopping z-score will be adjusted if the effective sample size is not equal to 200, 400, 600, or 800 by first finding the cumulative probability of stopping that corresponds to the *effective sample size.* This will be accomplished using linear interpolation (or extrapolation for the first analysis.)

Then the stopping z-value for efficacy at the ith analysis will be found so that the cumulative spending function will equal the cumulative probability of stopping under the null hypothesis. The stopping z-value for futility will be found so that the cumulative probability of stopping under the alternative hypothesis will be preserved in the same manner as for the efficacy stopping rule.

8 Data Collection and Site Monitoring

8.1 Data Collection

Each site will have a lap-top computer. The research coordinator will be responsible for maintaining a data base using a custom designed data base application. Once a week the research coordinator will connect his/her computer to a modem. The coordinating center computer will call the site computers during the evening and download the active database from each site. The software is designed with a series of checks to avoid missing or incorrect data.

8.2 Reporting of Adverse Events

Adverse events shall be reported as described in Appendix B.

8.3 Site Monitoring

Routine site visits will be performed no more than once each year to ensure that all regulatory requirements for the use of investigational agents are being met and to monitor the quality of the data collected. The site visit team will be composed of a research nurse and other members of the Clinical Coordinating Center, a representative of the NHLBI and an investigator from another CCTG. Records of IRB approvals and patient charts will be examined as needed to evaluate the accuracy of the data entered into the database.

9 Risk Assessment

1. Patients in the 6 ml/kg treatment group will probably experience more hypercapnia and may experience worse shunt ([14]). Therefore, they may require higher FiO_2's to achieve the target PaO_2 or SpO_2, which could lead to some increased risk of oxygen toxicity. Patients in the 12 ml/kg treatment group will have higher airway pressures,

consistent with the higher levels of lung stretch and potential for barotrauma.

2. Hypercapnia and respiratory acidosis in the 6 ml/kg tidal volume group may require more sodium bicarbonate to maintain arterial pH targets. This could cause volume overload or hypernatremia. However, fluid balance and serum sodium are assessed frequently in the intensive care units. The potential adverse effects of bicarbonate infusions can be anticipated and avoided, minimized, or counteracted with diuretics and adjustments in fluid management.

3. 6 ml/kg tidal volume patients may experience more dyspnea, for which they would receive more sedation. Generous sedation (benzodiazepines and narcotics) is given to most critically ill patients because of anxiety and discomfort. Additional sedation requirements in the 6 ml/kg tidal volume group will likely be small.

10 Human Subjects

All protocols will require that all study participants or a member of a patient's family sign and date an informed consent. All protocols will require prior IRB approval before any subject is entered into the study. All study participants or their families will be informed about the objectives of the study and the potential risks. All laboratory specimens, evaluation forms and reports will be identified by a coded number only to maintain patient confidentiality. All records will kept in a locked/password protected computer. All computer entry and networking programs will require coded numbers. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, National Heart, Lung, and Blood Institute and ARDS Clinical Coordinating Center (per 21CFR sec. 50 and 312). Layered informed consent for genetic testing of biological samples will be obtained as outlined in Appendix E.

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11 Appendices

A Exclusion criteria definitions

7. Conditions where hypercapnia-induced elevations in intracranial pressure should be avoided:
   - Intracranial bleeding
   - GCS ≤ 8
   - Cerebral contusion
   - Cerebral edema
   - Mass effect (midline shift on CT scan)
   - Papilledema
   - Intracranial pressure monitoring
   - Flat EEG for 48 hours
   - Fixed pupils
   - Absence of responses to deep pain
   - "Severe, terminal CNS damage"
8. Severe Chronic Respiratory Disease
   - FEV_1 less than 20 ml/kg IBW (e.g. 1.4 L for a 70 kg person), or
   - FEV_1/VC less than 50% predicted, or
   - Chronic hypercarbia ($PaCO_2$ greater than 45 mmHg) and/or chronic hypoxemia ($PaO_2 < 55$ mmHg) on $FiO_2 = 0.21$ or
   - Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
   - Hospitalization within the past six months for respiratory failure ($PaCO_2 > 50$ mmHg or $PaO_2 < 55$ mmHg or O_2-Sat $<$ 88% on $FiO_2 = .21$).
   - Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, e.g., unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean PAP > 40 mmHg), or respirator dependency.

16. Liver Failure: Child-Pugh Class C, which is defined as a total of $\geq$ 10 points on the following scoring table ([37]).

    Use the table to assess severity of abnormalities in each of the five clinical variables. Add the numerical scores.

Points	Class
5-6	A
7-9	B
$\geq$ 10	C

	Numerical score for increasing abnormality		
Measurement	1	2	3
Ascites	None	Present	Tense
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (sec. prolonged)	1-4	4-10	> 10

B Adverse Event Reporting Procedure

1. Procedures for Reporting Adverse Events

   Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. All adverse events will be evaluated by the Principal Investigator. The Study Coordinator must view patient records for possible, unexpected, adverse events throughout the study period. All serious adverse events occurring within the study hospitalization must be reported in the participants' case report forms.

   The investigator will report all **serious**, unexpected, and study-related adverse events to the Clinical Coordinating Center within 24 hours. The institutional review board must also be informed in a timely manner. The investigator will then submit a detailed written report to the Clinical Coordinating Center and the Institutional Review Board no later than 5 days after the investigator discovers the event.

2. Definition of Adverse Events

   A **serious** adverse event is any event that is fatal or immediately life-threatening, is permanently disabling, or severely incapacitating or requires or prolongs inpatient hospitalization.

   Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include the reaction that, had it occurred in more serious form, might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

   An **unexpected** adverse event is any experience not identified by type, severity, or frequency in the current study protocol, investigators brochure, or clinical safety updates or an event unexpected in ARDS or more severe or frequent than expected in ARDS.

   Please note that organ failures related to ARDS or the patient's underlying condition should not be reported as adverse events since they are systematically captured by the protocol.

SCHEDULE OF EVENTS

NIH ARDS Network Ventilator Trial

(see ARDSNet 03 for other required items)

DAYS	0	1	2	3	4	7	14	21	28
Demographics, History & Physical	X								
Vital Signs[R] (until two days unassist. vent. or ICU discharge)	X	X	X	X	X	X	X	X	X
Blood and Urine Tests: S_pO_2[R] (when ventilated)	X	A	A	A	A	A	A	A	
ABG's (when ventilated)	X	A	A	A	A	A	A	A	A
Na^+, K^+, Cl^-, HCO_3^-, Glu, BUN	X	A	A	A					
Albumin	X								
Creatinine	X	A	A	A	A	A	A	A	A
Hct/Hgb, WBC, Diff., Platelets	X	A	A	A	A	A	A	A	A
HCG[F]	X								
Blood for Cytokines	X	X		X					
Chest X-ray Score/Barotrauma	A	A	A	A	A	A	A	A	A
Glasgow Coma Score[R]	X					X	X	X	X
Ventilator Parameters[R]	X	X	X	X	X	X	X	X	X
Weight	A	A	A	A	A	A	A	A	
Height	X								
Fluids In and Out (when ventilated)	X	X	X	X	X	X			
Hemodynamics[R]	A	A	A	A					
Medications (Paralytics, Sedatives, Vasopressors)	X	X	X	X	X	X			

X = Required
A = When Available
[R] = Measured during daily reference measurements; other values may be obtained at 8 a.m. ± 12 hours. When more than one value is available, the value obtained closest to 8 a.m. will be recorded.
[F] = Required on females of reproductive age.

D Oxygenation Goals

- **Arterial oxygenation higher than the target range:**

  FiO_2 or PEEP will be decreased (by .10 or 2.0, respectively), whichever is farther (number of step changes) from the target scale shown in the accompanying table. If both PEEP and FiO_2 are equally distanced from the scale, then PEEP will be decreased.

- **Arterial oxygenation lower than the target range:**

  FiO_2 or PEEP will be increased (by .10 or 2.0, respectively), whichever is farther from the target scale shown in the table. If both PEEP and FiO_2 are equidistant from the scale, then PEEP will be increased first.

- **Arterial oxygenation within the target range:**

  If a single adjustment in either FiO_2 or PEEP would correct the FiO_2/PEEP to the target scale, then FiO_2 will be adjusted.

  If the FiO_2/PEEP cannot be corrected to the target scale with a single adjustment, then FiO_2 will be adjusted by .10 and PEEP will be simultaneously adjusted in the opposite direction by 2.0. E.g.: increase FiO_2 by .10 and decrease PEEP by 2.0, or decrease FiO_2 by .10 and increase PEEP by 2.0.

OXYGENATION GOALS

Acceptable Oxygenation

$55 \leq PaO_2 \leq 80$ or

$88 \leq S_pO_2 \leq 95$

Use this table if a patient's PEEP and FiO_2 are not compatible with the protocol scale (page 24) and $PaO_2 > 80$ mmHg or $SpO_2 > 95\%$. Find the box that corresponds to the current PEEP/FiO_2 settings. Make the changes in PEEP or FiO_2 indicated in the box. The approved protocol PEEP/FiO_2 combinations are indicated by "*****".

FOR TRADITIONAL AND LOW STRETCH with PLATEAU PRESSURE < 30* GROUPS

CURRENT SETTINGS	FiO_2 0.3	FiO_2 0.4	FiO_2 0.5	FiO_2 0.6	FiO_2 0.7	FiO_2 0.8	FiO_2 0.9	FiO_2 1.0
PEEP 5	*****	*****						
PEEP 8		*****	*****					
PEEP 10			*****	*****	*****			
PEEP 12					*****			
PEEP 14					*****	*****	*****	
PEEP 16							*****	
PEEP 18							*****	*****
PEEP 20								*****
PEEP 22-24								Max. Rx.

* If PaO2 < 55 or $S_pO_2 < 95\%$ in Low Stretch Patient with Plateau Pressure ≥ 30, increase FiO_2 in steps of 0.1 to 1.0 prior to any PEEP increase.

***** = approved PEEP/FiO_2 combination.

E Genetic Testing Information

Portions of the blood or BAL samples collected, processed, and stored as specified in this protocol may be used for genetic analyses in the future. Genetic analysis will involve, in part, the analysis of genomic DNA and will attempt to link genotypic information to the extensive phenotypic information measured as part of this study. A layered informed consent will be used to obtain the study subjects' consent for genetic testing. Consent for the use of these samples for genetic analysis related to the study of ARDS by the ARDS Network Investigators, consent for future studies not necessarily related to ARDS, or consent for genetic testing in both of these categories will be obtained. The level of an individual's consent for testing (e.g. none, for ARDS studies, for future studies, or all studies) will be recorded in the Case Report Forms and stored in the Clinical Coordinating Center Data Base.

Samples are stored at a central repository per ARDS Network protocol. Samples are identified by their ARDSNet Study Numbers. Approved studies for genetic testing will be sent to the CCC where samples that have the necessary level of informed consent for genetic testing will be identified. The CCC will then instruct the repository to prepare the relevant samples for shipment. The samples will have the ARDSNet Study Numbers removed and will be re-labeled with a new number. The Clinical Coordinating Center will be the only site to keep the database, relating the new sample number to the previous ARDSNet Study number, and this will be kept strictly confidential.

Upon completion of Network activities, the CCC will assign new Study Numbers for all ARDSNet Study subjects. The CCC will then instruct the repository to strip all samples of their ARDSNet identifiers and re-label them with the new study subject numbers. This will prevent investigators from using the ARDS Net Study Numbers to identify individual subjects in the future.

Overview of ARDSNet Study Procedures

Criteria	LaSRS (02)	ARMA (01)	Lisofylline (03)
Pre-Treatment Evaluations	electrolytes, BUN, creatinine, glucose, bilirubin, amylase, CBC, platelets, prothrombin time, serum albumin. (pregnancy test)	vital signs, ventilator parameters, weight, arterial PO_2, PCO_2, pH, SpO_2, urinary output (24 h) electrolytes, BUN, creatinine, glucose, CBC, platelets, albumin, glasgow coma score, (pregnancy test)	12-lead ECG, CBC, platelets, creatinine, BUN, albumin, electrolytes, glucose, total bilirubin, AST, ALT and alkaline phosphatase. (pregnancy test)
On Study Labs	Daily assessment, record **if available:** • Any positive culture • creatinine, bilirubin, platelets, prothrombin time, glucose • **Required on Day 7**: Amylase, glucose, total 24h insulin dose, total calorie intake, TPN	Days 1-4, 7, 14, 21, 28 • vital signs, • ventilator parameters, • fluids in/out, • medications (days 1-4, 7) Record if available: • electrolytes, BUN, glucose(days 1-3), • creatinine, CBC, platelets, ABGs, SpO_2,	Days, 1,2,3,4,7,14 and 21: vital signs, CBC, platelets, creatinine, BUN, albumin, electrolytes, glucose, total bilirubin, AST, ALT, alk phos.
Additional Labs			If creatinine > 2.5 or bilirubin >3.0, then draw drug levels daily for 3 days and then weekly until drug is discontinued.
Specimens	• BAL -baseline and day 7 • Plasma for cytokines, baseline and day 7.	• Plasma for cytokines on day 0 and day 3.	• Serum and plasma for surrogate markers and drug levels on day 0 and day 3. • Serum and plasma for surrogate markers (pre on day 0, pre/post day 3 • Plasma for drug levels- (pre/post and day 0 and day 3. • Plasma for cytokines on days

	LaSRS (02)	ARMA (01)	Lisofylline (03)
Ventilator Parameters	mode, FiO_2, V_T, PEEP, Pplat, Cst, V_{Ecorr}, patient position (daily through day 5, then weekly. ABG required on day 7.	Mode, ventilator rate, V_T(inspired), FiO_2, PEEP, Pplat (0.5 sec pause), ventilator manufacturer/model. Arterial PO_2, PCO_2, pH and SpO_2	.
Infection Monitoring	Monitor for infection to day 28 or for 7 days after drug discontinuation or death or discharge from study hospital		Monitor for infection to day 28 or death or discharge from study hospital
Dosing	Single dose of MPSS 2 mg/kg loading dose, then 0.5 ml/kg q6h x 14 days, then 0.5 mg/kg q12h x 7 days then tapered.		3 ml/kg to a maximum of 300 mg. Dose is q6h with 10 minute infusion.
Taper or Drug Discontinuation	Begin rapid taper if: patient develops: • disseminated fungal infection, • septic shock, or • reaches 48 hours of unassisted breathing.		Discontinue drug for: • unacceptable toxicity, • AEs associated with study drug, withdrawal by physician • withdrawal of consent by patient/family, • 2 consecutive days of unassisted breathing.
Forms to be Completed if Withdrawn from Study	ventilator parameters, vital signs, monitoring and medication, weaning	ventilator parameters, vitals signs, weaning form	ventilator parameters, vital signs, infection monitoring,
Adverse Events	All serious, unexpected and drug-related Adverse Events until discharge or day 60 if still in study hospital.	All serious, unexpected and study related Adverse events until discharge from study hospital.	All serious and unexpected Adverse Events from beginning of drug treatment through 14 days after last dose . All deaths that occur from beginning of drug tx to 60 days after study entry are reportable.

	LaSRS (02)	ARMA (01)	Lisofylline (03)
Death Report	When reporting a death, use #6 under item 2 on the adverse event form.	See death report under lisofylline (03)	All deaths to 60 days after study entry, regardless of location, should be reported. Complete death report form.
Endpoint (mortality)	Status at 60 days after study entry (if patient goes home alive, off vent, prior to day 60, s/he is considered "alive") Telephone follow-up of patients discharged home off-ventilation prior to day 60 is not required.	Status at 28 days from study entry. (If patient goes home alive, off vent prior to day 28, s/he is considered "alive".) If patient is still alive after day 28 but is not discharged home with unassisted breathing, check on patient status at intervals of ≤ 30 days until patient goes home on unassisted breathing or dies.	Status at 28 days from study entry and 60 days after drug discontinuation. Coordinators must contact patient or family to ascertain vital status at 28 and 60 days.
Miscellaneous		Blood still drawn for cytokines. Urine is no longer collected	ECG: Day 0 (prior to first dose) also on days 1, 7 and 21 within one hour of completion of infusion
	Monitoring/Meds form should be completed until day 28 or until patient is discharged, or dies.	Report all study deaths in hospital to day 180.	Monitoring/Meds form should be completed until day 28 or until patient is discharged or dies.

ARDS Clinical Coordinating Center
Massachusetts General Hospital
50 Staniford Street, Suite 560
Boston, MA 02114
Tel: (617) 724-3000
Fax: (617) 724-9878

March 25, 1999

Amendment II to ARDS Network Study 01, version III

On March 11, 1999, the Data and Safety Monitoring Board (DSMB) recommended that patients no longer be randomized to 12 ml/kg in ARDS Network Study 01. The recommendation was based on the results of the fourth (of five) planned interim analyses which revealed an estimated mortality of 30.4% in the 422 patients on the 6ml/kg arm and 39.8% in the 419 on the 12 mg/kg arm. The mortality difference crossed the predetermined efficacy stopping boundary.

Since March 16, 1998, mandatory coenrollment on ARDS Network Study 03 (The Lisofylline study) and Study 01 has been required as part of a factorial design. The DSMB recommended that patients enrolled into the Lisofylline study continue to be treated with the 6 ml/kg arm of the ARDS Network Study 01 protocol. Therefore, this amendment changes ARDS Network Study 01 version III to an observational trial with all patients treated with the 6 ml/kg arm of the protocol. Mandatory coenrollment and informed consent to participate in both ARDS Network Studies 01 and 03 will continue. Inclusion and exclusion criteria, enrollment time window, ventilator management procedures for 6 ml/kg tidal volume, data collection, adverse event reporting, sample collection, and DSMB review after every 200 patients will continue unchanged. This observational trial will continue until either Study 03 ends or the observational study is replaced by another randomized comparison of ICU methodology. Our purpose in maintaining the ventilator management arm calling for 6 ml/kg, other than its superiority over 12 ml/kg, is to provide continued standardization of the most important pulmonary support treatment in these patients