

**Prospective, Randomized, Multicenter Trial of Aerosolized
Albuterol Versus Placebo in Acute Lung Injury**

ARDS Clinical Network
ARDSNet Study 06 – Version II

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ABBREVIATIONS

AA = Arachidonic Acid
ALI = Acute Lung Injury
ARDS = Acute Respiratory Distress Syndrome
BPM = beats per minute
BAL = Bronchoalveolar Lavage
BMI = Body Mass Index
BUN = Blood Urea Nitrogen
CHF = Congestive Heart Failure
CPAP = Continuous Positive Airway Pressure
CPR = Cardiopulmonary resuscitation
CT = Computed Tomography
DBP = Diastolic Blood Pressure
DSMB = Data Safety Monitoring Board
FACTT = Fluid and Catheter Treatment Trial
FiO₂ = Fraction of Inspired Oxygen
GCS = Glasgow Coma Scale
ICU = Intensive Care Unit
IgA = Immunoglobulin A
IL-1 = Interleukin 1
IL-6 = Interleukin 6
IL-8 = Interleukin 8
IL-10 = Interleukin 10
IMV = Intermittent Mechanical Ventilation
INR = International Normalized Ratio

Home = Type of residence immediately prior to study hospitalization.
IVRS = Interactive Voice Response System
mBW = measured body weight
MHR = Maximum heart rate
NHLBI = National Heart Lung and Blood Institute
OR = Odds Ratio
PaCO₂ = Partial pressure of arterial carbon dioxide
PAI -1 = Plasminogen Activator Inhibitor 1
PaO₂ = Partial pressure of arterial oxygen
PAP = Pulmonary Artery Pressure
PB = Barometric Pressure
PBW = Predicted Body Weight
PCP = *Pneumocystis carinii* pneumonia
PEEP = Positive End-Expiratory Pressure
PGI₂ = Prostaglandin I₂
PIN = Personal Identification Number
Pplat = Plateau pressure
PS = Pressure Support Ventilation
SBP = Systolic Blood Pressure
SBT = Spontaneous Breathing Trial
SpO₂ = Oxygen Saturation
TNF = Tumor Necrosis Factor
VFD = Ventilator-free Days
WBC = White Blood Cell

Definitions

- **Completing 48 hours of UAB (from weaning form):** Defined as the date (calendar day) that the subject reaches exactly 48 hours of UAB. Example: if subject meets UAB at 1900 on 6/1/06 and does not return to AB, then the date of completing 48 hours of UAB would be 6/3/06.
- **Off protocol albuterol use:** Any patient who receives more than 30 mg of albuterol off protocol prior to study day 10 or ICU discharge will be considered a “too-frequently” off protocol subject. If this exceeds 10 % of enrolled patients in phase 2, then the SC will evaluate how this can be decreased to less than 5 percent of patients.
- **Date of first UAB (from Study Termination form):** Defined as the first day that the subject is on UAB from midnight to midnight. Example: if subject meets UAB at 1900 on 6/1/06, then the date of first UAB would be 6/2/06, as long as subject does not return to AB on 6/2/06.
- **Day zero:** Defined as day of randomization
- **Drug held/hold drug:** Study medication withheld for one treatment
- **Drug permanently discontinued:** Study medication stopped for remainder of the trial.
- **Drug temporarily discontinued:** Study medication with held for 24 hours
- **Duration of aerosolization:** Defined as the time from the beginning of aerosolization to 15 minutes after completion of aerosolization.
- **Resting heart rate:** Resting heart rate is a representative value of heart rate recorded on ICU source document (vital signs) in the 4 hours before screening.
- **Study Drug:** Defined as albuterol at either the 2.5 mg (reduced dose) or 5.0 mg (full dose) dose or placebo
- **Study withdrawal:** Defined as permanent withdrawal from study before completion of study activities. This **does NOT** include those subjects who have completed the protocol procedures or stopped procedures because they have reached unassisted breathing. If a patient or surrogate requests withdrawal from the study the clinician should seek explicit permission to continue data collection.
- **Sustained ventricular tachycardia:** Defined as an episode that lasts at least 30 seconds.
- **Uncontrolled diabetes mellitus:** Two or more glucose values in the previous 24 hours of 300 mg/dl or more.

- **Uncontrolled hypertension:** Mean arterial pressure (MAP) consistently greater than 110 mmHg in the preceding 4 hours, or MAP > 120 mmHg on 2 or more recorded values in the past 8 hours.

Part I Study Summary

- **Title:** Prospective, Randomized, Multicenter Trial of Aerosolized Albuterol Versus Placebo for the Treatment of Acute Lung Injury.
- **Objective:** To test the safety and efficacy of aerosolized beta-2 adrenergic agonist therapy (Albuterol Sulfate, USP) for improving clinical outcomes in patients with acute lung injury using a placebo controlled, double blinded randomized design.
- **Hypothesis:** Beta-2 adrenergic agonist therapy will improve clinical outcomes in patients with acute lung injury (ALI). The potential mechanisms for improved outcomes include a decrease in pulmonary inflammation, reduction in lung endothelial and epithelial permeability, and enhanced resolution of alveolar edema.
- **Study Design:** Phase II/III prospective, randomized, double-blind, placebo controlled trial
 1. Enrollment: approximately 36-48 months.
 2. In Phase II, patients will be treated with aerosolized albuterol 5.0 mg (n=40-50) versus normal saline placebo (n= 40-50) administered every 4 hours for 10 days following randomization or until 24 hours following extubation, whichever occurs first. The protocol stipulates that the 5.0 mg dose will be reduced to 2.5 mg if patients exceed defined heart rate limits. In Phase III, the 5.0 mg dose will be used unless there is evidence that this dose has an unacceptable safety profile or dose reductions for tachycardia occur in a large fraction of patients, in which case a lower dose of 2.5 mg will be used.
 3. Patients will be followed for 90 days or until discharge from the hospital to home with unassisted breathing, whichever occurs first.
- **Sample Size/Interim Monitoring:**
 1. The study will accrue a maximum of 1000 patients.
 2. Trial progress will be evaluated by the ARDS Network Steering Committee and an independent Data and Safety Monitoring Board (DSMB) following the enrollment of the first 100-120 patients for safety of the 5.0 mg dose of albuterol. After the enrollment of approximately 100, 250, 500, and 750 patients, the DSMB will evaluate the study for safety and efficacy of the dose determined in Phase II. Stopping for efficacy and futility will be based on preset stopping boundaries.
- **Inclusion Criteria:**

Patients will be eligible for inclusion if they meet all of the below criteria. Criteria 1-3 must all be present within a 24-hour time period:

Acute onset (defined below) of:

1. $\text{PaO}_2 / \text{FiO}_2 = 300$ (intubated). If altitude $> 1000\text{m}$, then $\text{PaO}_2 / \text{FiO}_2 = 300 \times (\text{PB}/760)$
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 for at least 12 hours, and
4. No clinical evidence of left -sided cardiac failure to account for bilateral pulmonary infiltrates.

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

The 48-hour enrollment time window begins when criteria 1-3 are met. If a patient meets the first three inclusion criteria but has a PAOP (Pulmonary Arterial Wedge Pressure) greater than 18 mmHg, then the first four criteria must persist for more than 12 hours after the PAOP has declined to ≤ 18 mmHg, and still be within the 48-hour enrollment window.

“Acute onset” is defined as follows: the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must be ≤ 28 days at the time of randomization. Opacities considered “consistent with pulmonary edema” include any opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (greater than 28 days). Vascular redistribution, indistinct vessels, and indistinct heart borders alone are not considered “consistent with pulmonary edema” and thus would not count as qualifying opacities for this study.

• **Exclusion Criteria:**

1. Age younger than 13 years
2. Greater than 48 hours since all inclusion criteria are met.
3. Neuromuscular disease that impairs ability to ventilate without assistance, such as cervical spinal cord injury at level C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barré syndrome or myasthenia gravis (see appendix A).
4. Pregnancy (negative pregnancy test required for women of child-bearing potential) or breast-feeding.
5. Severe chronic respiratory disease (see appendix A for detailed exclusion criteria)
6. Burns greater than 40% total body surface area
7. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50% (see appendix A)
8. Allogeneic bone marrow transplant within the last 5 years
9. Patient, surrogate, or physician 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).
10. Severe chronic liver disease (Child-Pugh Score of 11 -15)

11. Diffuse alveolar hemorrhage from vasculitis
 12. Morbid obesity (greater than 1kg/cm body weight).
 13. No consent/inability to obtain consent
 14. Unwillingness or inability to utilize the ARDS network 6 ml / kg PBW ventilation protocol
 15. Moribund patient not expected to survive 24 hours
 16. No intent to obtain central venous access for monitoring intravascular pressures.
 17. Contraindication to aerosolized albuterol (Appendix A.8)
 18. Daily use (prior to study hospitalization) of inhaled beta agonist, corticosteroid, or oral leukotriene modifier for reactive airway disease.
 19. Unwillingness of primary physician to discontinue inpatient beta agonist use.
 20. Acute myocardial infarction or acute coronary syndrome within 30 days
 21. Severe congestive heart failure (see appendix A5)
 22. Participation in other experimental medication trial within 30 days with the exception of the ARDSNet pharmacconutrient nutrition trial (OMEGA)
 23. Heart rate greater than 85% of maximal predicted heart rate (MGR85) as calculated by $MHR85 = 85\% \times (220 - \text{age})$ or 140 beats per minute (whichever is lower).
 24. Patients receiving high frequency ventilation.
 25. Atrial fibrillation (new since hospital admission) requiring anticoagulation.
 26. Greater than 5 PVCs per minute in the four hour period prior to randomization.
- **Safety:** The number of adverse events, including the proportion of patients in whom study drug was reduced in dosage and/or prematurely discontinued because of arrhythmia or other adverse events, will be evaluated in the first 100-120 patients to examine the response to the 5 mg albuterol dosing compared to the saline placebo arms. In addition, the proportion of patients requiring dose adjustments for tachycardia and the change from baseline heart rate and blood pressure will be compared between the placebo and 5.0 mg albuterol treatment groups. These safety endpoints will be used during the Phase II portion of the study to select the dose to be used in Phase III.
 - **Efficacy:** The primary efficacy variable for the phase III portion of the trial is the number of Ventilator Free Days (VFDs): the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. This is a composite endpoint reflecting days free of mechanical ventilation to day 28 and mortality. Patients who die before day 28 have zero VFDs.
 - **Secondary Efficacy Variables:**
 1. The secondary efficacy variable is mortality before discharge home, with unassisted breathing to day 60. Patients alive in hospital at day 60 will be considered to have survived.
 2. Mortality before hospital discharge home, with unassisted breathing, to day 90. Patients alive in hospital to day 90 will considered to have survived.
 3. Number of ICU-free days at 28 days after randomization.

4. Number of Organ Failure Free days at 28 days after randomization (hepatic, renal, cardiovascular, central nervous system, hematologic).
5. Number of days between the day of first meeting criteria for weaning-readiness (3.2.1) and day 28 after randomization.
6. Mortality and VFDs in patients with pre-randomization $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 200$.
7. Change in plasma and mini-bronchoalveolar lavage levels of IL-6, IL-8, VWF, SP-D and total protein concentrations from baseline and on study day 3.
8. Mortality prior to hospital discharge to day 60 and number of ventilator-free days to day 28 in patients with shock (defined in 2.1.2) at the time of randomization.
9. Change in baseline and post-treatment in the albuterol versus placebo treated patients in the physiological indices of lung injury including oxygenation (P/F ratio), alveolar-arterial oxygen difference, quasistatic respiratory compliance, dynamic respiratory compliance, plateau airway pressure, oxygenation index, and the acute lung injury 4-point score.

Part II Study Description

Prospective, Randomized, Multicenter Trial of Aerosolized Albuterol Versus Placebo in Acute Lung Injury

1. Background

Rationale based on prior studies. There is evidence from two clinical studies that impaired alveolar fluid clearance is associated with a higher mortality in patients with acute lung injury (Matthay, 1990; Ware, 2001b). This association of higher mortality and impaired lung epithelial fluid transport in clinical lung injury may be related to both the magnitude of pulmonary epithelial and endothelial injury and to down-regulation of specific ion and fluid transporters in the alveolar epithelium (Matthay, 2002). Although acute lung injury involves much more than just the accumulation of alveolar edema fluid (Ware, 2000), restoration of the alveolar epithelial fluid transport capacity of the lung to a normal level may limit alveolar edema and hasten the resolution of acute lung injury (Sznajder, 2001; Crandall, 2001; Mutlu & Sznajder, 2004).

Several experimental studies have demonstrated that beta-2 adrenergic agonists accelerate the rate of alveolar fluid clearance in sheep, dogs, rats and mice as well as in the *ex vivo* human lung (Matthay, 2002; Crandall, 2001; Campbell, 1999; Sakuma, 1994; Mutlu & Sznajder, 2005; Sakuma, 2006). In addition, cAMP stimulation upregulates fluid transport transiently in the presence of septic or hypovolemic shock and severe hydrostatic pulmonary edema (Pittet, 1994; Pittet, 1996; Lane, 1998; Frank, 2000; Fang, 2002). Also, beta-2 adrenergic agonists can enhance the resolution of alveolar edema in the presence of hyperoxic experimental lung injury (Lasnier, 1996; Garat, 1997; Saldias, 1999a). Beta-2 adrenergic agonists delivered via the airspaces can overcome the depressant effects of hypoxia on alveolar fluid clearance (Vivona, 2001). This effect probably is explained in part by increased traffic of ion transporters to the apical cell membrane (Planes, 2002; Dada & Sznajder, JCI, 2003).

There is evidence that cAMP agonists can decrease lung endothelial permeability in animal models of acute lung injury. Therapy with isoproterenol reduced thrombin induced endothelial

permeability both *in vitro* and *in vivo*, and the effects were mediated primarily by the beta-2 receptor (Minnear, 1989; Minnear, 1993). Activation of beta-adrenergic receptors reduced endothelial permeability in the systemic circulation (Dobbins, 1988). Beta-2 adrenergic agonist therapy in rat lungs injured with ischemia/reperfusion both reduced edema formation and enhanced the resolution of alveolar edema (Khimenko, 1994).

Furthermore, a variety of more recent *in vitro* and *in vivo* studies have explored the molecular basis for the anti-inflammatory effects of beta-adrenergic agonists. For example, beta-adrenergic agonists decrease endotoxin induced release of pro-inflammatory cytokines such as TNF- α in lung explants (Zhang, 1999) and during human endotoxemia (Van der Poll, 1996). These effects may be mediated in part by decreasing endotoxin induced activation of the transcriptional factor, NF κ B (Farmer, 2000). Beta-adrenergic stimulation can inhibit the procoagulant effects of endotoxin (Pajkrt, 1997). In these studies, epinephrine decreased circulating thrombin-anti-thrombin complexes (TATc), suggesting that adrenergic agonists may have beneficial effects on coagulopathic cascades associated with infection that may be involved in the development and progression of ALI. Also, administration of dobutamine to rats after LPS injection diminished pulmonary IL-6 levels (Dhingra, 2001).

One recent human study demonstrated anti-inflammatory properties of beta-2 agonist therapy. In a recent article in the *AJRCCM*, pretreatment with an inhaled beta-2 agonist markedly reduced neutrophil influx, neutrophil de-granulation, and accumulation of tumor necrosis factor alpha in the airspaces of human volunteers exposed to inhaled endotoxin (Maris, 2005).

In addition to a large number of animal studies that support the basic mechanisms described above, some clinical studies have particular relevance to this proposal. For example, a randomized, placebo controlled trial of mechanically ventilated patients with ARDS examined the effect of a standard beta-2 agonist (metaproterenol) given by aerosol in patients with lung injury (Wright, 1994). Aerosolized beta-2 agonist significantly reduced peak airway pressure and airflow resistance. In addition, there was a significant decline in plateau airway pressure suggesting an improvement in total respiratory system compliance

A beta-2 adrenergic agonist (salmeterol) was reported to reduce the incidence of high altitude pulmonary edema (HAPE) in HAPE-susceptible patients in a double blind placebo controlled randomized trial (Sartori, 2002a). The beta-2 agonist may have upregulated the fluid transport capacity of the alveolar epithelium. Experimental studies show that beta-2 agonists can overcome hypoxia induced depression of alveolar fluid clearance (Vivona, 2001; Planes, 2002). However, in this study of HAPE susceptible subjects, the beta-2 agonist may have also lowered pulmonary artery pressure or increased minute ventilation. Both of these effects may have accounted for reduced pulmonary edema in the HAPE-susceptible patients treated with inhalation of salmeterol.

Until recently, there were no data to assess the effect of beta-agonist therapy on lung fluid balance in patients. However, in a recent publication, Perkins and colleagues reported the results of a clinical trial of 40 patients with acute lung injury in which the effects of beta-agonists were examined. Salbutamol (albuterol) was administered intravenously at a dose of 15 μ g/kg/hour in a double blind, randomized manner. Extravascular lung water on day 7, the primary outcome variable, was lower in the salbutamol-treated patients compared with the placebo control subjects

(9.2 vs. 13.2 ml/kg, $p = 0.04$). *Post hoc* analysis indicated that extravascular lung water was significantly lower in the treated group at earlier time points as well. Plateau airway pressure was also 6 cm H₂O lower at day 7 in the salbutamol-treated group ($p = 0.049$), and there was a trend toward lower acute lung injury scores in the salbutamol-treated patients. This study did report a high number of supraventricular arrhythmias in the patients treated with intravenous salbutamol, a safety issue of some concern, and one of the reasons why this trial is designed to use aerosolized albuterol as explained and rationalized below.

Evidence for adequate concentrations of albuterol when administered by the aerosol route.

In order to determine if aerosolized beta-2 agonist would actually reach the alveolar compartment in an intubated, ventilated patient with pulmonary edema, albuterol concentrations were analyzed in the pulmonary edema fluid and plasma of 22 patients who were treated approximately every 4 hours with aerosolized albuterol sulfate USP (Atabai, 2002). The patients had pulmonary edema either from a hydrostatic cause ($n=10$) or from acute lung injury ($n=12$). After a total aerosolized dose of 3.5 ± 2.6 mg in the prior 6 hours, the concentration in pulmonary edema fluid (obtained by direct suction with a 14 French gauge catheter without saline dilution) was 1,240 ng/ml (10^{-6} M), a concentration that is on the plateau of the dose response curve for upregulating alveolar fluid clearance in the *ex vivo* human lung (Sakuma, 1997). Plasma albuterol levels were much lower with a median concentration of 10^{-8} M. The data from this observational study suggest that continuous albuterol administration would not be necessary and an appropriate dosing interval would be every 4 hours, perhaps with as low as 2.5 mg of nebulized albuterol (Atabai, 2002).

Selection of the dose of aerosolized albuterol for this trial. Because aerosol delivery through an endotracheal tube is often reduced compared to delivery through natural airways (MacIntyre, 2002, Dhand, 1997), and because it is imperative that adequate drug reaches the alveolar spaces, initial dosing in this study will be a 5 mg/dose of albuterol. This dose is commonly used safely in endotracheally intubated patients for bronchodilation and should reliably supply alveolar levels of albuterol at or above the concentration noted above. A survey of clinical practice was performed among academic university hospitals (University Hospital Consortium) to determine the practice patterns for use of 5 mg of aerosolized albuterol in acutely ill patients. A 5 mg dose given every four hours was the most commonly used in two of the 15 centers (13%). In addition, the 5 mg dosage was part of clinical practice in 9 of the 15 centers (60%). Based on the Atabai study cited above, a 2.5 mg aerosolized albuterol dose would likely achieve sufficient levels in the edema fluid and distal airspaces of the lungs in ALI/ARDS patients. However, the higher dose of 5.0 mg would be preferable since there would be more certainty that therapeutic levels would be achieved. If, however, we should learn that the 5.0 mg dose has adverse events associated with it or results in heart rate limited dose reductions in a substantial fraction of patients, then the trial can go forward with the lower 2.5 mg albuterol dose. The first interim analysis of 100-120 patients will assess the safety of the **5.0 mg** dose to determine its appropriateness as the sole dosing regimen for the remainder of the study, as discussed in section 5.1.

Alternatives to beta agonists for the treatment of rhonchi and wheezes in critically ill patients. The frequency of use of beta-2 agonists in the care of patients with ALI is unknown, although they are often used in patients when rhonchi or wheezes are appreciated on clinical examination, not necessarily only in patients with known asthma or COPD. It is important to

indicate that routine pulmonary toilet with suctioning of the airways is a reasonable first step. If the clinical findings do not clear with suctioning the aerosolized ipratropium could be used as an alternative to beta agonists for bronchospasm. Because clinical studies and clinical practice indicate that ipratropium (given either as an aerosol or metered dose inhaler) is used widely for treatment of bronchospasm in critically ill patients in the United States (Dolovich, 2000) we anticipate minimal use of off study albuterol use in this study, with less than 5% of patients receiving albuterol at some point in their clinical course. The frequency of off study albuterol use will be examined in the Phase II period of the trial.

Potential confounding issues in a clinical trial of beta-2 agonists for acute lung injury.

There are several potential confounding issues in a clinical trial of beta-2 adrenergic agonists for treatment of clinical lung injury. The first is the potential impact of endogenous or exogenous catecholamines. In one recent study, the levels of epinephrine and norepinephrine measured in the plasma of patients with early acute lung injury were often in a normal range and were markedly elevated in less than 15 % of patients (Ware, 2001b). It would be expected that these elevated levels would decline in most patients with the institution of therapy for shock and sedation. Also, the elevated levels in the plasma would not in most cases achieve the optimal therapeutic levels for beta-2 stimulation that seem to be appropriate for upregulating alveolar epithelial fluid transport to a maximal level (Sakuma, 1997; Sakuma, 2006). In patients with ALI, treatment with vasoactive agents for supporting blood pressure, especially norepinephrine, epinephrine, and dobutamine, may also confound the analysis because these agents have some beta-2 adrenergic agonist properties. However, dobutamine is usually used for treatment of low cardiac output associated with heart failure and is not often used for patients with acute lung injury. Epinephrine is used primarily in refractory shock. Norepinephrine is used in more patients with septic shock than epinephrine or dobutamine, but it mainly stimulates beta-1 receptors. There is some experimental evidence that beta-1 stimulation can increase alveolar fluid clearance but norepinephrine did not stimulate alveolar fluid clearance in a recent study of *ex vivo* human lungs (Sakuma, 2006). Therefore, it is anticipated that the confounding effect of these vasoactive agents will be minimal, especially since the study drug will be given over 10 days. Also, based on an analysis of the FACTT trial, the total number of vasopressor days was 20.3% for the 10 days following enrollment. Another possible related confounding treatment is the use of dopamine, an agent that can increase alveolar fluid clearance when delivered into the airspaces of the lung (Matthay, 2002; Salidas, 1999b). Dopamine is usually given in doses in the systemic circulation (2-10 ug/kg/min) that are well below those used experimentally to augment alveolar fluid clearance. Also, dopamine is not known to have the anti-inflammatory anti-permeability properties of beta-2 agonists. Furthermore, the use of dopamine as a treatment for oliguric renal failure has recently been shown to be ineffective so low dose dopamine may be utilized significantly less than in some prior studies (Clinical Trials Group, 2000; Holmes, 2003).

A second concern is that beta-adrenergic agonist therapy might result in down-regulation of beta-receptors during the 7 days of the clinical trial. This has been an issue in patients being treated for months with asthma (Barnes, 1995). Recent experimental work in mice and rats suggests that this would not be a significant issue in this clinical study. In one rat study, there was no attenuation of beta receptor stimulation of alveolar fluid clearance with high dose intravenous epinephrine in rats for 4 hours (Charron, 1999) although a more recent study suggested some decrease in cAMP stimulated fluid clearance in rats after exposure to high dose isoproterenol for several days (Morgan, 2001). However, in a mouse study, albuterol administration in high doses

over 6 days did not reduce the absolute rate of alveolar fluid clearance stimulation with intra-alveolar terbutaline (Sartori, 2002b). Also, in the recent Perkins clinics trial, lung water was reduced over 7 days with albuterol treated groups suggesting downregulation did not occur (Perkins, 2006).

Potential side effects of aerosolized beta-2 agonist therapy. The use of even aerosolized beta-2 adrenergic agonists may precipitate systemic hemodynamic instability, particularly tachycardia or cardiac arrhythmias. Albuterol will be given by aerosol inhalation and the concentrations in the systemic circulation will be two orders of magnitude lower than in the lung (Atabai, 2002). In general, the safety experience with aerosolized beta-2 agonists in critically ill patients is very favorable. Most clinicians do not perceive that their use is associated with serious side effects. On the basis of the Atabai study (Atabai, 2002), we know from personal communication from the authors that there were no changes in heart rate, systolic blood pressure, or diastolic blood pressure during albuterol treatment or one hour after treatment. These data were gathered retrospectively and therefore were not included in the published manuscript.

Two studies provide support for the conclusion that the use of inhaled beta-2 agonists is not associated with adverse cardiac effects. In one study, 24 patients with known coronary artery disease and clinically stable asthma or chronic obstructive pulmonary disease were monitored after treatment with different doses of inhaled albuterol, including 5 mg given with a nebulizer (Rossinen, 1998). No cardiac symptoms were associated with albuterol inhalation, and there was no change in the systolic blood pressure in any patients. Electrocardiographic monitoring revealed no evidence of ischemia or ventricular arrhythmias (Rossinen, 1998). In a more recent article, the Saskatchewan Health Services Databases were used to form a population based cohort of all patients with newly diagnosed COPD over the age of 55 years identified between 1980 and 1997 (Suissa, 2003). All subjects were followed up until 1999, death, or the first occurrence of acute myocardial infarction. The cohort consisted of 12,090 patients including 1127 cases with fatal or nonfatal acute myocardial infarction. The adjusted rate ratio for current use of inhaled beta agonists was 1.12% and 1.02 % for first time use. There was no significant increase in risk for fatal or nonfatal myocardial infarction when the analysis was restricted to subjects with cardiac risk factors such as hypertension, diabetes mellitus, or to subjects not having been prescribed beta blocker medicines (Suissa, 2003).

There are certain conditions where albuterol or a beta-2 agonist is contraindicated including severe hypokalemia. However, the conduct of this trial will monitor carefully for any adverse side effects and, as noted above, there is a plan to determine if aerosolization of 5.0 mg of albuterol will be well tolerated in acute lung injury patients.

Biological end-points. The NIH ARDS Network has completed the study of several biochemical markers in their initial 6 vs. 12- ml/kg tidal volume trial (ARDS Network, 2000). Most of these data have been published in manuscript form. In brief, interleukin-6, interleukin-8 and surfactant protein D levels in the plasma are favorably affected by a lung protective tidal volume strategy of 6 ml/kg IBW compared to 12 ml/kg IBW. Also, elevated plasma levels of von Willebrand factor-Antigen (VWF), a marker of endothelial injury or activation, is a strong independent predictor for death in ALI patients based on both single center data (Ware, 2001a) and the NIH multicenter trial (Ware, 2004). Since cAMP agonist therapy may reduce lung endothelial permeability, it is reasonable to measure plasma and mini-BAL levels of VWF as

well as IL-6 and IL-8 (markers of inflammation) and SP-D (a marker of epithelial barrier permeability) at baseline and after 3 days to monitor for a favorable biologic effect of albuterol treatment in this study. The levels of VWF in ALI/ARDS patients are increased to high levels by inflammation and endothelial injury. Therefore, we anticipate that a beneficial effect on systemic and/or endothelial permeability may be reflected by a decline in VWF plasma and mini-BAL levels in the albuterol treated patients as well as a reduction in the mini-BAL levels of total protein. Mini-BAL will provide direct measurements in the lung that can reflect pulmonary specific changes in permeability and inflammatory responses in the same way in which the recent Maris study showed impressive changes in the BAL of normal volunteers who were challenged with endotoxin and then treated with an inhaled beta-2 agonist or placebo (Maris, 2005). We will also measure the concentration of protein in BAL as an index of pulmonary permeability to protein, a well-established index of lung injury and a correlate of high mortality (Clark, 1995). Also it is important to note that mini-BAL has been shown to reflect similar changes in total protein and myeloperoxidase concentrations in the distal airspaces of the lung in patients with acute lung injury compared to the results with traditional fiberoptic bronchoscopy guided BAL (Perkins, 2006).

Clinical end points. The primary outcome variable is an increase in ventilator free days. This outcome has been selected because it has clinical significance and because albuterol treatment is expected to reduce lung edema by both decreasing edema formation and enhancing the resolution of alveolar edema. We would anticipate therefore that indices of lung function that may show improvement with albuterol therapy would be oxygenation, lung compliance, oxygenation index (product of mean airway pressure and oxygenation), peak and plateau airway pressures, and a composite assessment of lung injury (4-point lung injury score). An improvement in these pulmonary indices would be expected to correlate with more ventilator free days.

Measurement of Long Term Outcomes and Acute Lung Injury. Emerging data indicate that survivors of acute lung injury have substantial disability after recovery from acute lung injury. After hospital discharge, only about one-third return to home and more than one-half reside in skilled nursing facilities or rehabilitation facilities (Rubenfeld, 2005). Up to one year later, most patients have serious deficits in health-related quality of life, functional performance, cognition, and employment (Herridge, 2003; Hopkins, 2005). Mortality and ventilator-free days, which have been the primary outcomes in most clinical trials of treatments for acute lung injury, do not capture these important longer-term decrements (Brower, 2004; ARDSNet, 2000; Schoenfeld, 2002). Moreover, it has recently become clear that acute lung injury, contrary to previous belief, becomes a chronic, disabling pulmonary condition in many cases (Herridge, 2003). To capture the full impact of any treatment for acute lung injury, longer-term outcomes must be assessed.

The effects of treatment for acute lung injury on short-term mortality may not capture the full impact of treatment over the longer term. A treatment may have early benefit that is maintained, amplified, or attenuated over a longer time period. For example, an invasive strategy for diagnosing ventilator-associated pneumonia reduced 14 day mortality, but the benefit decreased thereafter and the mortality benefit was lost (Fagon, 2000). In addition, a treatment may improve mortality but have additional deleterious effects that adversely affect long-term outcomes such as health-related quality of life and functional performance. For example, parenteral corticosteroids, which may have some immediate benefit in late-phase ARDS, may have detrimental longer-term

effects on muscle function and weakness that lead to impaired physical functioning (Herridge, 2003). To fully evaluate new therapies for acute lung injury, a broad spectrum of long-term outcomes must be ascertained. Moreover, measurement of long-term outcomes is necessary to compare the cost-effectiveness of different strategies for ARDS (Angus, 2001). Aerosolized beta-agonist therapy, if successful, will reduce the duration of positive pressure ventilation in survivors of acute lung injury. This effect would mean less sedation and less time in the intensive care unit, favorable outcomes that may translate to longer-term improvements in functional performance, cognition, and overall health-related quality of life.

Potential influence of genetic variation in beta receptor polymorphisms on the response to albuterol therapy. It is well known that there is marked interindividual variation in response to beta agonists (Drazen, 1996; Drazen, 1999) and that at least part of that interindividual variation is related to genetic differences in the beta-2 adrenergic receptor (BAR) and its related modulatory protein (beta adrenergic receptor upstream peptide – BUP) (Parola, 1994; McGraw, 1998; Green, 1995; Turki, 1996;). Polymorphisms and haplotypes of the BAR are associated with bronchodilator response to beta-adrenergic agents such as albuterol (Martinez, 1997; Lima, 1999; Ohe, 1995). Furthermore, polymorphisms of the BAR can also be associated with the magnitude of an individual's tachyphylaxis to beta agonists (Tan, 1997; Israel, 2000). The BAR binds beta agonists and mediates their actions in multiple tissues including the lung. The BAR gene is intronless and is located on chromosome 5q 31-32. There are relevant single nucleotide polymorphisms (SNP's) at -1023, -709, -654, -468, -406, -367, -47, -20, 46, 79, 252, 491, and 523 that define 12 haplotypes (Drysdale, 2000), of which three are common in Caucasians and five are common in African Americans (Drysdale, 2000). SNP's and SNP haplotypes of BUP and BAR have recently been shown to correlate with beta agonist-induced bronchodilation. Bronchodilator response varies between haplotypes of the BAR by over 200% (Drysdale, 2000). Responsiveness associated with individual haplotypes ranges from hyporesponsive to normal to hyperresponsive.

The actions of beta-adrenergic agents can vary between individuals depending upon an individual's SNP/haplotype of the BAR and BUP. Some studies in asthma patients have suggested that responses to bronchodilators over a period of weeks may be different in patients with an arginine-arginine versus a glycine-glycine receptor profile (Drazen, 1996; Drazen, 1999). However, in these studies there was no evidence of a difference in acute responses to bronchodilators in the different genotypes. In this trial, we encourage ancillary research protocol to collect blood for DNA analysis for determining haplotypes of the beta-adrenergic receptor are associated with a favorable response to albuterol in acute lung injury. A secondary hypothesis would be to determine if these genetic differences correlate with the proposed clinical outcomes, although there may not be enough power for this analysis in this trial.

Summary. Aerosolized beta-2 agonist therapy is anticipated to decrease pulmonary inflammation, diminish the formation of lung edema and enhance clearance of lung edema in patients with acute lung injury. Because beta-2 agonists have well demonstrated anti-inflammatory properties that can reduce permeability induced lung injury, it is anticipated that the severity of lung injury and the quantity of protein rich edema will be reduced by aerosolized beta-2 agonist therapy. In addition, beta-2 agonist therapy is expected to enhance the resolution of pulmonary edema by upregulating alveolar epithelial fluid transport mechanisms that will in turn enhance the clearance of alveolar edema. A reduction in the severity of lung injury and the

quantity of alveolar edema should result in improved pulmonary oxygen uptake, improved lung compliance, earlier extubation and more ventilator free days.

Although there may be also be a beneficial effect on survival, this trial is powered to test for an improvement in ventilator free days in part because a much larger trial would be needed to test for a significant improvement in mortality. However, as in the FACTT trial (NHLBI, 2006), we anticipate that it is feasible to achieve a greater number of ventilator free days with albuterol therapy and for this improved lung function to be associated with at least a trend for reduced mortality.

2. Clinical Value and Equipoise

The preceding section summarized animal studies and clinical studies suggesting the potential clinical benefits of the administration of beta₂-agonists to critically ill patients with ALI and ARDS. There are no large randomized, placebo control studies that have validated these purported benefits associated with aerosolized beta-2 agonists. Hence, intensivists are uncertain of the efficacy of these agents in treating non-bronchospastic sequelae of ALI and ARDS. Consequently, there is genuine uncertainty in the scientific community regarding whether beta-2 agonists are better than no therapy.

2.1. End-Points

2.1.1. Phase II End –Points

The primary safety endpoints for Phase II will be the number of adverse events and the proportion of patients who had study drug reduced in dosage and/or prematurely discontinued because of arrhythmia or other adverse events. In addition, the number of patients who require dose adjustments for tachycardia will be compared between the placebo and 5.0 mg treatment groups.

2.1.2. Phase III End-Points

Primary Outcome Variable

The number of ventilator free days (VFD). This is a composite endpoint including days free of mechanical ventilation to day 28 and mortality. VFD to day 28 is defined as the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28 unless a period of assisted breathing was less than 24 hours and the purpose of assisted breathing was a surgical procedure. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFD will be zero. Patients transferred to another hospital or other health care facility prior to day 28 while still receiving assisted breathing will be followed to assess this efficacy measure. Unassisted breathing is defined in section 2.2.2. VFDs is related to the “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 days of assisted ventilation would be misleading. “Average duration of ventilation in survivors” would avoid this potential problem. However, if there were a trend towards lower mortality in one treatment group with greater days of assisted ventilation in survivors in that group, the measure of days of assisted ventilation in survivors would be misleading. VFDs will be favorably affected by both lower mortality and shorter duration of ventilation in survivors.

Secondary Outcome Variables

1. The secondary efficacy variable for the phase III portion of the trial is mortality prior to hospital discharge with unassisted breathing. Patients alive in hospital at day 60 will be considered to have survived.
2. Mortality before hospital discharge home, with unassisted breathing, to day 90. Patients alive in hospital to day 90 will be considered to have survived
3. Number of ICU-free days at 28 days after randomization
4. Number of Organ Failure Free days at 28 days after randomization (hepatic, renal, cardiovascular, central nervous system, and hematologic) (Bernard, 1997).
5. Number of days between the day of first meeting criteria for weaning-readiness (section 3.2.1) and day 28 after randomization.
6. Mortality and VFDs in patients with pre-randomization $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 200$.
7. Change in plasma and mini-BAL levels of IL-6, IL-8, VWF, SPD, and total protein concentrations from baseline to study day 3.
8. Ventilator free days and mortality prior to hospital discharge with unassisted breathing to day 60 and number of ventilator-free days to day 28 in patients with shock (defined in 2.1.2) at the time of randomization.

Change from baseline in the albuterol versus placebo treated patients in the physiological indices of lung injury including oxygenation (P/F ratio), alveolar-arterial oxygen difference, quasistatic respiratory compliance, dynamic respiratory compliance, plateau airway pressure, oxygenation index, and the acute lung injury 4-point score will be analyzed.

Organ failure is defined as present on any date when the most abnormal vital signs or clinically available lab value meets the definition of clinically significant organ failure according to the Brussels Organ Failure Table. Patients will be followed for development of organ failures to ICU discharge or study day 28; whichever comes first. Each day a patient is alive and free of a given clinically significant organ failure will be scored as a failure-free day. Any day that a patient is alive and free of all five organ failures will represent days alive and free of all organ failure. Central nervous system dysfunction is evaluated using the Glasgow Coma Scale.

Rationale for Primary and Secondary Outcome Variables

The selection of ventilator-free days as the primary end-point for this study is based on the decision that an increase in ventilator-free days of two or more days would constitute a substantial decrease in morbidity from acute respiratory failure secondary to acute lung injury. It is also recognized that the therapy to be tested in this clinical trial, inhaled albuterol (a β -2 agonist) is likely to be safe and well tolerated by critically ill patients. Therefore, evidence that ventilator-free days was significantly increased by two days or more in this population would be received by intensive care clinicians as a significant advance in therapy. In addition, it is important that the therapy with β -2 adrenergic agonist be associated with no increase in mortality. Therefore, the initial secondary outcome is specified as mortality prior to hospital

discharge with unassisted breathing. Please see the section on statistical analysis to further address the issues of how these two outcomes – ventilator-free days and mortality – will be assessed in interim and final analyses in this trial. The other secondary endpoints reflect clinically important outcomes, physiologic variables that reflect the severity of ALI and the potential response to therapy with inhaled albuterol, as well as biologic end-points that will provide mechanistic insight into the how albuterol improved lung function. Secondary endpoints will be presented and the primary manuscript reporting the study results and will allow the scientific community and clinicians to judge the consistency of the findings. Accordingly, the secondary endpoints must be selected *a priori* so that a plan for analysis of the data is constructed prior to the possibility of bias, i.e., to avoid *post hoc* analyses that have not been pre-specified.

2.1.3 Secondary Objective

To develop and analyze a clinical database of patients enrolled in the clinical trial who are well characterized and followed 12 months for the purpose of answering questions about the natural history of ARDS and evaluating the effect of different interventions and patterns of supportive care.

2.2. Study Population and Enrollment

2.2.1. Patient Enrollment

The trial will accrue a maximum of 1000 patients over approximately 36-48 months. Enrollment estimated to be at least 2 patients per month from 12 sites.

Patients who are mechanically ventilated will be recruited from intensive care units. Permission to approach patients and/or their families will be requested from the attending physicians. De-identified demographic and physiologic data from all patients meeting the study inclusion criteria will be entered on a screening form. The screening form will also include information explaining why patients meeting the inclusion criteria were not enrolled (e.g. exclusion criteria, attending physician refusal, etc.). A list of the de-identified data collected on screened but not enrolled patients is included in Appendix E.

2.2.2. Inclusion Criteria

Patients will be eligible for inclusion if they meet all of the below criteria. Criteria 1-3 must all be present within a 24-hour time period:

Acute onset (defined below) of:

1. $\text{PaO}_2 / \text{FiO}_2 = 300$ (intubated). If altitude $> 1000\text{m}$, then $\text{PaO}_2 / \text{FiO}_2 = 300 \times (\text{PB}/760)$
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 for at least 12 hours, and
4. No clinical evidence of left -sided cardiac failure to account for bilateral pulmonary infiltrates.

The 48-hour enrollment time window begins when criteria 1-3 are met. If a patient meets the first three inclusion criteria but has a PAOP (Pulmonary Arterial Wedge Pressure) greater than 18 mmHg, then the first four criteria must persist for more than 12 hours after the PAOP has declined to = 18 mmHg, and still be within the 48-hour enrollment window.

“Acute onset” is defined as follows: the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must be \leq 28 days at the time of randomization. Opacities considered “consistent with pulmonary edema” include any opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (greater than 28 days). Vascular redistribution, indistinct vessels, and indistinct heart borders alone are not considered “consistent with pulmonary edema” and thus would not count as qualifying opacities for this study.

2.2.3. Exclusion Criteria

1. Age younger than 13 years
2. Greater than 48 hours since all inclusion criteria are met.
3. Neuromuscular disease that impairs ability to ventilate without assistance, such as cervical spinal cord injury at level C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barré syndrome or myasthenia gravis (see appendix A).
4. Pregnancy (negative pregnancy test required for women of child-bearing potential) or breast-feeding.
5. Severe chronic respiratory disease (see Appendix A)
6. Burns greater than 40% total body surface area
7. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50% (see appendix A)
8. Allogeneic Bone marrow transplant within the last 5 years.
9. Patient, surrogate, or physician 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).
10. Severe chronic liver disease (Child-Pugh Score of 11 -15)
11. Diffuse alveolar hemorrhage from vasculitis
12. Morbid obesity (greater than 1kg/cm body weight).
13. No consent/inability to obtain consent
14. Unwillingness or inability to utilize the ARDS network 6 ml / kg PBW ventilation protocol
15. Moribund patient not expected to survive 24 hours
16. No intent to obtain central venous access for monitoring intravascular pressures
17. Contraindication to aerosolized albuterol (Appendix A.8)

18. Daily use (prior to study hospitalization) of inhaled beta agonist, corticosteroid, or oral leukotriene modifier for reactive airway disease.
19. Unwillingness of primary physician to discontinue inpatient beta agonist use.
20. Acute myocardial infarction or acute coronary syndrome within 30 days
21. Severe congestive heart failure (Appendix A5)
22. Participation in other experimental medication trial within 30 days with the exception of the ARDSNet pharmacconutrient nutrition trial (OMEGA)
23. Heart rate greater than 85% of maximal predicted heart rate (MHR85) as calculated by $MHR85 = 85\% \times (220 - \text{age})$ or 140 beats per minute (whichever is lower).
24. Patients receiving high frequency ventilation.
25. Atrial fibrillation (new since hospital admission) requiring anticoagulation
26. Greater than 5 PVCs per minute in the four hour period prior to randomization.

Patients less than 13 years of age are excluded because delivery of albuterol may not be uniform, particularly with uncuffed endotracheal tubes. Patients with ALI for more than 48 hours are excluded to evaluate more clearly the effects of albuterol early in the course of lung injury. Exclusion criteria 3 and 5 confound the ventilator free day endpoint. Pregnancy is an exclusion because beta agonists may interfere with uterine contraction. Exclusion criteria 6-11 exclude patients unlikely to survive to the primary study endpoint. Patients with alveolar hemorrhage from vasculitis are excluded because the mechanism of lung injury is different from ALI and diffuse alveolar damage. Patients with contraindications to albuterol and acute myocardial infarction within 30 days are excluded because of a potential excess risk. Patients with congestive heart failure are excluded because of concerns about ventricular arrhythmias. Exclusion criterion 18 excludes patient who may need aerosolized beta-2 agonists during routine clinical care. Patients with a baseline heart rate of greater than 85% of maximal predicted heart rate are excluded, because a further increase in heart rate may be deleterious (see Appendix A.7 for details). Patients ventilated with high frequency ventilation are excluded because dosing of nebulized albuterol during these modes of ventilation is unreliable. Patients on beta blockers who would otherwise qualify for the study will not be excluded because aerosolized albuterol is expected to have sufficiently high lung concentrations to overcome the effects of oral or systemic beta blocker therapy.

2.2.4. Enrollment, Randomization, and Study Initiation Time Window

All patients must be enrolled and randomized within 48 hours of meeting the first three inclusion criteria. The last inclusion criterion may be met at either a network hospital or a referring hospital. The first aerosol treatment of study drug must be given within 4 hours of randomization. The day of randomization will be considered study day zero.

2.2.5. Informed Consent

Written informed consent will be obtained from each patient or surrogate. Patients who regain decision-making capacity prior to discharge from the study hospital will be asked to provide written consent for ongoing participation in the study.

2.2.6. Co-Enrollment

Patients on this study may be co-enrolled in the EDEN-OMEGA study. The randomization to both studies will occur at the same time.

2.2.7. Randomization

After obtaining a signed and dated informed consent, the coordinating center will be called and an assignment, in the form of a study ID number, will be made by computer-generated randomization to albuterol or placebo. If patients are co-enrolled on the EDGEN-OMEGA study the randomization will occur at the same time.

Randomization will be accomplished with a web based randomization system. Each research coordinator will have a unique Personal Identification Number (PIN). The randomization will provide a patient ID number to the pharmacy that will dispense either active treatment, or placebo based on a predetermined list in the research pharmacy. The pharmacist will be unblinded to the treatment assignments. He or she will be responsible for treatment assignments, formulations, and maintaining the list of codes revealing which treatment is being taken by each study participants.

The randomization will be stratified by institution, and by shock at study entry. If the patient is to be enrolled in the ALTA study alone they will be randomized between Albuterol vs. Placebo. If they are co-enrolled they will be randomized between eight treatments, Albuterol or Placebo combined with each of the four Early vs. Late or Nutriceutical vs. Placebo feeding treatment combinations.

2.2.8. Minorities, Women, and Children

Gender and racial 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 (22% black, 11% Hispanic, 2% Asian/pacific islander) 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.

Children will be enrolled who are 13 years and older. There is general agreement that children in this age range have pathophysiology and outcomes similar to adults with ALI. In addition the study procedures called for in the protocol can be readily carried out safely and effectively in this population.

Blinded 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 the intervention in the proposed study.

3. Study Procedures

3.1. Aerosol Study Procedures

3.1.1. Study Drug Dose

Albuterol sulfate, USP, solution for inhalation will be diluted as follows:

- The full dose of 5.0 mg (1.0 ml of 0.5% albuterol solution for inhalation, pH 3 - 5) will be diluted into 2.0 ml of sterile normal saline solution (0.9% sodium chloride without preservative, pH 4.5-7).
- The reduced dose of 2.5 mg (0.5 ml of 0.5% albuterol solution for inhalation, pH 3 - 5) will be diluted into 2.5 ml of sterile normal saline solution (0.9% sodium chloride without preservative, pH 4.5-7).

Placebo aerosol will consist of 3.0 ml of identical appearing sterile 0.9 % sodium chloride without preservative.

Only unit dose albuterol sulfate for inhalation without preservatives will be used in this study.

3.1.2. Treatment Period

The study drug will be given every 4 hours (plus or minus one hour) for ten days following randomization or until ICU discharge or 24 hours after extubation, whichever occurs first. For example, if a patient is randomized at 1500 on day zero and remains intubated then study drug would be given until 1500 on study day ten. If a patient is randomized at 1500 and is extubated at 1200 on study day 3, study drug would be continued until 1200 on study day 4. If a patient is re-intubated before ten days following randomization, the study drug will be restarted until ten days following randomization or 24-hours after extubation, whichever occurs first. For patients who have a tracheostomy, the equivalent of extubation for the purposes of this protocol will be breathing via tracheostomy with unassisted breathing as defined in 3.2.4.

3.1.3. Nebulizer Device, Technique and Ventilator Adjustments

A high-efficiency small volume jet nebulizer (SVN) powered at a flow of 8 liters/minute from a 50 psi wall oxygen flow meter will be used for continuous nebulization (e.g.: throughout the inspiratory and expiratory cycle). See Appendix F for details and references regarding the acceptable devices that must be used in this study – currently there are 4 acceptable nebulizers that generate uniform aerosol particles in the respirable range, have acceptable aerosol volume output, and deliver the same inspired dose to the distal and to the artificial airway during nebulization. The nebulizer will be placed proximal to the Y-connector in the inspiratory limb of the circuit with an 18 cm aerosol tubing reservoir to enhance drug delivery. Five mg of albuterol will be placed in the nebulizer cup and diluted with saline to a fill volume of 3 mL (this reduces

the amount of albuterol in the dead volume). The anticipated nebulization time given a 3 mL fill volume and a gas flow of 8 L/min is less than 13 min and the nebulization treatment should be discontinued within a few minutes after nebulizer “sputtering” is recognized by the clinician (i.e. the point at which aerosolization becomes erratic). Clinicians are encouraged to tap the nebulizer several times once sputtering begins in an attempt to increase drug nebulization and reduce dead volume.

Prior to nebulization, patients should be suctioned if necessary to assure minimal secretions are present in the airways. During nebulization, the ventilator’s inspiratory flow will be adjusted to produce an I:E ratio of 1:1 (without air trapping) during the nebulization to maximize delivery of the aerosol. Clinicians also have the option to adjust the flow rate if necessary for patient comfort. The nebulizer will be driven with the same fraction of inspired oxygen being delivered through the ventilator (if available) or with 100% oxygen (e.g., not room air).

It is important that when HMEs are used for humidification, they must be removed from the circuit during the nebulizer treatment to insure adequate drug delivery. When heated humidifiers are used, it has been recommended that the temperature be reduced or turned-off during the treatment to enhance drug delivery. Data supporting this practice is controversial, however, and thus it is only optional for ICUs that routinely do this.

It is recognized that the additional gas flow from the medication nebulizer will increase the delivered tidal volume. However, we recently tested the effects of nebulizer flow rates of 6 and 8 L/min in a mechanical lung model simulating mean ventilator settings and pulmonary mechanics reported from ARDS Network ARMA and ALVEOLI studies. We found that the effects on tidal volume (1-1.4 mL/kg increase) and Pplat (2 cm H₂O increase) were acceptable when the inspiratory time was 0.75 sec and in the context of a treatment time less than 15 min at a frequency of Q-4 hours. A recent survey of usual care practices at hospitals that will be participating in ALTA has revealed that 95% do not reduce tidal volume during an aerosol medication treatment on a routine basis. Temporary reductions in tidal volume could be considered if this practice is part of usual care or if the peak airway pressure rises above 35 cm H₂O. Because the additional flow from the nebulizer may affect some ventilator’s flow and volume monitoring capability, care must be taken by the clinicians to assure safe monitoring and proper alarm function during the nebulization.

3.1.4. Dose Interruptions and Adjustment for Tachycardia

Hold Parameters for Heart Rate Prior to and During Study Drug Aerosolization

Heart rate will be monitored continuously by a bedside monitor.

MHR=220-age

- 1) Do not give scheduled study drug dose if sustained pretreatment HR is greater than either 140 or 85% of MHR whichever is lower. If heart rate exceeds this threshold reassess heart rate at the next scheduled treatment time.
- 2) If during nebulization HR is greater than either 140 or 85% of MHR whichever is lower, stop the current treatment and reassess heart rate at the next scheduled treatment time.

Thus, if any of the above heart rate conditions are met, the aerosol will be held and the patient will be reassessed for suitability to receive study drug again in four hours:

Because fluctuations in heart rate during critical illness may be multifactorial (pain, general stress response, alterations in acid base status), the ICU team will evaluate the patient and a cause for tachycardia other than study drug will be sought and if identified, treated. The next scheduled aerosolization of the **full dose** of study drug will then be given and if the heart rate increases to the above thresholds a second time, the aerosol will be held and subsequent study drug doses will be reduced to 0.5 ml (2.5 mg of albuterol or saline) with 2.5 ml diluent (referred to subsequently as reduced dose). If heart rate increases to the above thresholds on two consecutive **reduced** study drug doses, study drug will be held for 24 hours and restarted at the reduced dose. A subsequent increase in heart rate to the above thresholds will result in the study drug being held for another 24 hours and restarted at the **reduced** dose. Any subsequent increases in heart rate to the above thresholds will result in **discontinuation of study drug for the duration of the study**. With this approach, a patient may not tolerate study drug in the first 48 hours, even at half the initial dose, but then still be able to receive the study drug from day three to ten.

Because several clinical studies show that inhaled beta-2 agonists do not result in significant hypotension or hypertension, we have not specifically established boundaries for albuterol dose adjustments for systemic blood pressure. Furthermore, alterations in blood pressure are more likely to be related to other clinical events (sepsis for example) or pharmacologic therapies (sedation). If episodes of hypertension or hypotension occur in temporal association with study drug dosing and are unexplained or unexpectedly severe for the usual course of a patient with ALI, these events would be reported as adverse events.

If patients develop more than 5 ventricular premature contractions (PVCs) per minute during aerosolization of the study drug, then the dose will be stopped. This is the threshold used in the Goldman and Desky criteria for pre-operative risk assessment (Goldman, 1977; Desky, 1986). The next treatment will be with the **reduced** dose of the study drug. If there is a recurrence of the PVCs at more than 5/minute, then the study drug will be held for 24 hours and restarted at the **reduced** dose. Any subsequent recurrence of the PVCs at more than 5/minute during aerosolization will mandate **permanent withdrawal of the study drug for the duration of the study**. Episodes of PVCs greater than 5/min that occur between doses of study drug should be treated as though they occurred during aerosolization; the next scheduled treatment should be a reduced dose if the previous treatment had been a full dose.

In patients who develop sustained atrial arrhythmias after study entry, including new onset atrial fibrillation, atrial flutter, supraventricular tachycardia, or multifocal atrial tachycardia, the study drug will be held for 24 hours and the event will be reported as an adverse event. After 24 hours the study drug can be restarted at the **reduced** dose if the patient's physician judges that an atrial arrhythmia has been adequately treated and is under control. The drug will be permanently withdrawn for any episode of ventricular tachycardia or ventricular fibrillation. Eligible patients with preexisting atrial fibrillation or multifocal atrial rhythms with a controlled ventricular response may participate in this trial with the following exception: a patient with **new onset** atrial fibrillation (onset occurred after study hospital admission) requiring anticoagulation is NOT eligible to participate in this trial. For enrolled patients with pre-existing atrial fibrillation

or multifocal atrial rhythms, study drug will be dosed and subsequently adjusted, held, or discontinued based on change in baseline heart rates as described in the above paragraph. However, if a patient develops **new onset** atrial fibrillation requiring anticoagulation after randomization, the patient should not receive any further study drug.

3.1.5. Management of Bronchospasm During the 10-day Treatment Period

The intent of exclusion criteria #18 is to exclude patients with a history of bronchospasm who require daily treatment before study entry. However, some patients may develop signs of bronchospasm while on-study, including wheezes noted on auscultation of the chest, rising peak airway pressures, evidence of air trapping, or increasing peak to plateau (static) airway pressure difference. Because retained airway secretions and a mal-positioned endotracheal tube may cause some of these findings, patients will receive airway suctioning and confirmation of proper endotracheal tube position per standard local ICU procedures.

In subjects with persistent findings of bronchospasm, the use of aerosolized ipratropium at a dose and frequency routinely used at the study ICU would be an option. The decision to use ipratropium for bronchospasm will be made by the patient's physician considering the best interests of the patient. If a physician wishes to administer aerosol beta agonist during the 10-day study drug administration period, then the prescribing physician will make assessment of the clinical response to one treatment. If the prescribing physician decides to continue treatment with an aerosol beta agonist for another 12 hours (i.e., 3 more doses), then again the physician will be required to reassess the need for aerosol beta agonist therapy after the next 12 hours. Study drug should be held during a trial of non-study beta-agonist for bronchospasm. Study drug can resume 4 hours after the last dose of non-study beta-agonist. The use and dose of non-study aerosolized beta-agonists will be recorded in the case report forms.

3.1.6. Dose Interruptions for Hypokalemia

Beta agonists may produce hypokalemia due to movement of potassium into intracellular stores. Hypokalemia is usually mild and transient, and serum potassium levels are frequently measured in clinical care. Patients will be excluded from participation if the serum potassium is less than or equal to 3.0 mEq/L and does not correct with treatment. Patient may be enrolled if the serum potassium level increases to greater than 3.0 mEq/L with potassium supplementation as part usual clinical care, as long as patient is still in the 48-hour enrollment window. For patients on-study, study drug will be held if a potassium level, determined by clinical care, falls to less than or equal to 3.0 mEq/L. Study drug will be restarted if the potassium level increases to greater than 3.0 mEq/L.

3.1.7. Premature Discontinuation of Study Drug Administration

Permanent discontinuation of the study drug is defined as cessation of the study drug without the intent of restarting the study drug during the ten-day treatment period. Patients who have their study drug permanently discontinued will continue their participation in the study, and will be followed to determine their vital status to hospital day 90 or hospital discharge, as outlined in the Schedule of Events (Appendix B).

Permanent discontinuation of the study drug aerosol will occur in the following situations:

- New onset of sustained atrial arrhythmia (atrial fibrillation requiring anticoagulation, atrial flutter, supraventricular tachycardia, multifocal atrial tachycardia) refractory to treatment as specified in section 3.1.4.
- Ventricular fibrillation or sustained ventricular tachycardia (sustained ventricular tachycardia defined as an episode lasting at least 30 seconds).
- If the patient experiences serious adverse events *related to the study drug* as described in section 6.2.1.
- If the investigator, attending physician, the patient or their surrogate decides that the study drug should be discontinued. If this decision is made because of an adverse event, then appropriate adverse event reporting procedures should be followed.

3.2. Ventilator Procedures

A modified, simplified version of The ARDS Network lung protective lower tidal volume strategy will be used in this trial. This strategy, which was associated with unprecedented low mortality rates in three previous ARDS Network trials (ARMA, ALVEOLI, and FACTT), will ensure that study subjects receive the beneficial effects of lung protection as part of their participation in this trial (The Acute Respiratory Distress Syndrome Network, 2000, Brower, 2003). ARDS Network personnel have substantial experience in the application of this protocol from the three completed trials noted above.

1. Any mode of ventilation capable of delivering the prescribed tidal volume (6ml/kg PBW, +/- 2ml/kg) may be used, provided the V_T target is monitored and adjusted appropriately. During APRV, tidal volume is defined as the sum of the volume that results from the ventilator pressure-release and an estimation of the average spontaneous V_T .
2. Tidal Volume (V_T) goal = 6 ml/kg Predicted Body Weight.
3. Measure and record inspiratory plateau pressure (Pplat) according to ICU routine (at least every four hours and after changes in V_T and PEEP recommended).
4. If Pplat greater than 30 cm H₂O, reduce V_T to 5 ml/kg and then to 4 ml/kg PBW if necessary to decrease Pplat to less than or equal to 30.
5. If V_T less than 6 ml/kg PBW and Pplat less than 25, raise V_T by 1 ml/kg PBW to a maximum of 6 ml/kg.
6. If "severe dyspnea" (more than 3 double breaths/minute or airway pressure remains at or below PEEP level during inspiration), then raise V_T to 7 or 8 ml/kg PBW if Pplat remains below 30. If Pplat exceeds 30 on 7 or 8 ml/kg PBW, then revert to lower V_T and consider more sedation.
7. If pH less than 7.15, V_T may be raised and Pplat limit suspended (not required).
8. Oxygenation target: PaO₂ = 55-80 mm Hg or SpO₂ = 88-95%.
9. Minimum PEEP = 5 cm H₂O.
10. Adjust F_IO₂ or PEEP upward within 5 minutes of consistent measurements that are below the oxygenation target range.
11. Adjust F_IO₂ or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.
12. No specific rules for how to use PEEP and F_IO₂ (except for minimum PEEP of 5). The lower PEEP/higher FiO₂ table represents a consensus approach developed by ARDSNet

investigators in 1995. Most ARDSNet centers have used this table in the past 10 years and are comfortable with it. The higher PEEP/lower F_{iO_2} table yielded equivalent results in a randomized trial (Brower, 2003) and would be acceptable and perhaps preferable in patients who appear to respond with substantial increase in arterial oxygenation in the transition from lower to higher PEEP.

Lower ELV/Higher F_{iO_2} Treatment Group

F_{iO_2}	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Higher ELV/Lower F_{iO_2} Study Group

F_{iO_2}	.30	.30	.30	.30	.30	.40	.40	.50	.50	.50 – .80	.80	.90	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

- (Levels of PEEP in these F_{iO_2} /PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.)
- No specific rules for respiratory rate. Recommend to raise respiratory rate in increments to 35/minute (maximum set rate) if pH less than 7.30.
- No specific rules about I:E. Recommend that duration of Inspiration be less than or equal to duration of Expiration.
- Bicarbonate is allowed (neither encouraged nor discouraged) if pH less than or equal to 7.30.

3.2.1. Weaning

Patients will be assessed for the following weaning readiness 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 six hours.

1. At least 12 hours since enrollment in the trial.
2. F_{iO_2} = 0.40 and PEEP = 8 cm H_2O or F_{iO_2} = 0.50 and PEEP = 5 cm H_2O .
3. Values of both PEEP and F_{iO_2} = values from previous day (comparing Reference Measurement values).
4. Not receiving neuromuscular blocking agents and without neuromuscular blockade.
5. Patient exhibiting inspiratory efforts. If no efforts are evident at baseline, ventilator set rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts.
6. Systolic arterial pressure greater than or equal to 90 mmHg without vasopressor support (= 5 microgram/kg/min dopamine or dobutamine will not be considered a vasopressor).

If criteria 1-6 are met, then initiate a trial of up to 120 minutes of spontaneous breathing with F_{iO_2} = 0.5 using any of the following approaches:

1. Pressure support = 5cm H_2O , PEEP = 5cm H_2O
2. CPAP = 5 cm H_2O
3. T-piece

4. Tracheostomy mask

Monitor for tolerance using the following:

1. SpO₂ = 90% or PaO₂ = 60 mmHg.
2. Mean spontaneous tidal volume = 4 ml/kg PBW, if measured.
3. Respiratory rate = 35/min.
4. pH = 7.30, if measured.
5. No respiratory distress (2 or more of the following):
 - a. Heart rate greater than or equal to 120% of the 0600 rate (less than or equal to 5 min at greater than 120% may be tolerated).
 - b. Marked use of accessory muscles.
 - c. Abdominal paradox.
 - d. Diaphoresis.
 - e. Marked subjective dyspnea.

If any of goals 1-5 are not met, revert to previous ventilator settings or to Pressure Support (PS) greater than or equal to 10 cm H₂O with Positive End-expiratory Pressure and F₁O₂ = previous settings and reassess for weaning the next morning.

The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

3.2.2. Decision to remove ventilatory support

For intubated patients, if tolerance criteria for spontaneous breathing trial (1-5 above) are met for at least 30 minutes, the clinical team may decide to extubate. However, the spontaneous breathing trial can continue for up to 120 minutes if tolerance remains in question. If any of criteria 1-5 are not met during unassisted breathing (or 120 minutes has passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean will be restored and the patient will be reassessed for weaning the following day.

3.2.3. 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 greater than 28 days elapsed since enrollment.

3.2.4. Definition of Unassisted Breathing

1. Extubated with face mask, nasal prong oxygen, or room air, OR

2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to 5 cm H₂O without pressure support or IMV assistance.

3.3. On-Study Fluid Management

Fluid management during shock will be unrestricted. However, in patients not in shock, a conservative fluid approach will be required for all patients enrolled in the study. This conservative fluid management approach will represent a simplification of the algorithm utilized in the ARDS Network FACTT study (see Appendix I). If not already being utilized, this conservative fluid management approach must be initiated within four hours of randomization and continued until UAB or study day seven, whichever occurs first.

3.4. Glucose Management

The network recognizes the importance of maintaining blood glucose levels in a reasonable range. The plan is to allow each hospital to use their own protocol for glucose and insulin administration but the target is to maintain the blood glucose less than 150 mg/dl and greater than 80 mg/dl. The use of protocols with tighter ranges of blood sugar control (i.e. 80 - 110 mg / dl) will be allowed at institutions where this is standard practice for the care of critically ill patients.

4. Data Collection

The following will be collected in the four-hour interval that precedes randomization. If more than one variable is available during the four-hour interval, the last value will be recorded. For items required in the APACHE III score, the highest or lowest values, per APACHE III rules, will be collected in the 24-hour period preceding randomization. The baseline chest radiograph is the pre-randomization radiograph used to meet inclusion criteria (qualifying radiograph).

4.1. Background Assessments

1. Pregnancy test (serum or urine) for women of childbearing potential
2. Demographic and admission data
3. Pertinent medical history and physical examination
4. Height and measured weight
5. Time on ventilator prior to enrollment
6. Type of admission
 - a. Medical
 - b. Surgical scheduled
 - c. Surgical unscheduled
7. Risk factors for ALI/ARDS (sepsis, aspiration, trauma, pneumonia, drug overdose, other)
8. Presence of following chronic diseases:
 - a. Metastatic cancer

- b. Hematologic malignancy
- c. AIDS

4.2. Baseline Assessments

1. Vital signs: heart rate (b/min), systemic systolic, diastolic, and mean blood pressure (mm Hg), and body temperature (degrees C).
2. Ventilator mode, tidal volume, minute ventilation set respiratory rate and total respiratory rate, peak, plateau, mean airway pressure, and inspiratory flow rate/profile.
3. $F_{I}O_2$, PaO_2 , $PaCO_2$, pH, and SpO_2 (qualifying arterial blood gas)
4. Central venous pressure if a central venous line is in place
5. Fluid intake, fluid output (most recent 24 hour value) or mean hourly value for most recently available period
6. Serum electrolytes, glucose, albumin, and total protein
7. Blood hemoglobin, prothrombin time (PT), International Normalized Ratio (INR), platelet count
8. Glasgow Coma Score
9. Frontal chest radiograph (qualifying radiograph)
 - a. Radiographic lung injury score (# of quadrants)
10. Administration of following medications:
 - a. Vasopressors and inotropic agents (including dose)
 - b. Beta blockers
11. Presumed site of infection, if sepsis is the etiology of ALI/ARDS.
12. Blood for DNA banking (appendix D)
13. Blood for cytokines, mediators, and markers of inflammation. Plasma obtained from two, 10 ml blood samples will be divided immediately after centrifugation into 4 equal 2 ml aliquots in specified tubes and frozen at $-70^{\circ}C$.
14. Urine for leukotriene B series and F_2 - isoprostane metabolites. Urine obtained from the patients will be collected a 8 ml sample tube and divided into 4 equal aliquots in specified tubes and frozen at $-70^{\circ}C$.
15. Bronchoalveolar lavage fluid for levels of IL-6, IL-8 and protein. BAL fluid will be obtained from a mini-BAL procedure (see Appendix K), divided into 4 equal aliquots of 2 ml each in specified tubes, and frozen at $-70^{\circ}C$.
16. Plasma for epinephrine levels will be collected in a 5 ml purple top tube and placed into a single aliquot of 2.5-3.5 ml on the first 100 ALTA subjects.
17. Dead-space measurements at selected sites.

4.3. Assessments During Study

The following parameters will be measured and recorded daily from 6:00-10:00 am using the values closest to 8:00 am (except where indicated) on the study days indicated in the Schedule of Events (Appendix B).

1. If receiving positive pressure ventilation:
 - a. Mode

- b. PEEP level
 - c. Peak, plateau, and mean airway pressures
 - d. Respiratory rate, tidal volume, minute ventilation
 - e. Inspiratory flow rate and profile
2. $F_{I}O_2$, PaO₂, PaCO₂, pH, and SpO₂
 3. Central venous pressure
 4. Hemodynamic values
 - a. Systemic arterial systolic, diastolic, and mean pressure
 - b. Heart rate (beats/minute)
 5. Fluid intake in past 24 hours
 6. Fluid output in past 24 hours
 7. Serum electrolytes, creatinine
 8. Blood hemoglobin concentration, prothrombin time (PT), International Normalized Ratio (INR), platelet count
 9. Administration of the following:
 - a. Beta agonist aerosol
 - b. Beta blockers
 - c. Intravenous beta agonists (dobutamine, norepinephrine, epinephrine, dopamine; including dose)
 10. Brussels score
 - a. Worst PaO₂/ $F_{I}O_2$ for that date
 - b. Worst systolic blood pressure for that date
 - c. Worst creatinine, bilirubin, and platelet count for that date
 - d. Use of vasopressors
 11. Blood for cytokines, mediators, and markers of inflammation. Plasma obtained from two, 10 ml blood samples will be divided immediately after centrifugation into 4 equal 2 ml aliquots in specified tubes and frozen at $-70^{\circ}C$. Blood will be collected on days 0 and 3.
 12. Plasma epinephrine levels will be measured on a plasma sample obtained at baseline and on study days 0 and 1 in the first 100 ALTA subjects.
 13. Urine for leukotriene and isoprostane metabolites. Urine obtained from the patients will be collected in two, 8 ml sample tubes and divided into 4 equal aliquots in specified tubes and frozen at $-70^{\circ}C$. Urine will be collected on days 0 and 3.
 14. Mini-Bronchoalveolar lavage fluid for levels of IL-6, IL-8, and protein. Mini-BAL fluid will be divided into 4 equal aliquots in specified tubes and frozen at $-70^{\circ}C$. Mini-BAL fluid will be collected from all patients who are still intubated on study day 3.

15. Plasma albuterol levels will be measured on Day 1 in the first 100 subjects. Samples will be obtained 15 minutes after completion of a dose of study drug during the Phase II portion of the trial.
16. Vital status at 28, 60, and 90 days until discharged home on UAB.
17. Pre-dose heart rate (representative value for the 5 minutes before each study drug dose) and blood pressure (measured within 5 minutes of initiation of study drug) and maximal heart rate (from time aerosolization begins to 15 minutes after completion of the aerosol) and blood pressure at 15 minutes post dose for all doses of study drug to day 10 or 24 hours after extubation, whichever occurs first.
18. On-study occurrence and treatment of atrial fibrillation.
19. Dead-space measurements at selected sites.

4.4. Assessments after Hospitalization

As explained in the Background and Significance section of this proposal, it is very important to obtain long term outcomes data on the patients enrolled in this ALTA trial and the Nutrition trial as either or both interventions may have a significant effect on long term morbidity, and it would be very unfortunate to carry out a large trial of this kind and have no mechanism to determine longer term outcomes.

The following data, as well as vital status, will be collected at 3, 6 and 12 months after ICU discharge. We will collect this data through telephone interviews with patients. In addition, we will verify duration of survival for patients lost to follow-up or noted to have died using the Centers for Disease Control and Prevention's National Death Index (NDI). We will use each patient's social security number (SSN) for an exact NDI match. We will collect contact information for the patient and alternative contact information on up to 3 individuals. This information and the SSN will be collected on paper at the time of consent, and forward via secure fax to the CCC. Contact information and SSN will be maintained on paper and will not appear in the CCC database.

The following instruments will be used in data collection. This battery of instruments will be piloted test guarantee feasibility. The text explains the alternative tests available pending the results of the pilot testing.

1. Health-related Quality of Life:
 - a. SF-36 (consider the SF-12 if the length is too long in pilot testing). *Estimated administration time: 6 minutes.*
 - b. Euro-QOL (EQ-5d): *Estimated administration time 2 minutes.*
 - c. Functional Assessment of Chronic Illness Therapy (FACIT; 13 questions) (if length is too long in pilot testing, this instrument will be deleted due to over-lap with SF-36); *Estimate administration time: 3 minutes*

2. Psychological Outcomes:
 Depression and Anxiety: Hospital Anxiety and Depression Scale (14 questions)
Estimated administration time: 5 minutes
 - a. Post-Traumatic Stress Disorder (PTSD): Impact of Events Scale—Revised (22 questions); *estimated administration time: 3 minutes.*

3. Neurocognitive Outcomes: Telephone version of the Mini-Mental State Examination (TMMSE) (16 items); *Estimated administration time: 5 minutes*

4. Physical Activity Outcomes:
 - a. Overall: Functional Performance Inventory-Short Form (32 questions) (alternative: deleting this instrument (due to overlap with the Physical Function Domain of SF-36) or use the Katz ADL (6 questions) & the Lawton IADL, 8 questions, if length is too long in pilot testing) *Estimated administration time: 5 minutes*
 - b. Work disability: Return to Work Custom-made Questionnaire (12 questions—will reduce number of questions if length is too long in pilot testing); *Estimated administration time: 2 minutes.*

5. Health care utilization: Custom-made instrument developed based on University of Toronto ARDS Outcome Study instrument provided by Margaret Herridge (27 questions), will reduce number of questions if this instrument is too lengthy in pilot testing; *Estimate administration time: 8 minutes*

4.4 Other data collected

Pre-morbid conditions including:

- a. APACHE III Demographics plus history of: hypertension, prior myocardial infarction, congestive heart failure, peripheral vascular disease, prior stroke with sequelae, dementia, chronic pulmonary disease, arthritis, peptic ulcer disease
- b. Survey of smoking history including:
 - Ever smoker (>100 cigarettes in lifetime)? Y/N
 - If Yes, current smoker? Y/N
 - If ever smoker, estimate pack years:
 - Pack years = (# packs per day) x (number of years smoked)
 - If former smoker, when quit?
- c. Survey of alcohol history (see Appendix L)

5. Statistical Considerations

Primary Endpoint

The primary endpoint will be ventilator free days. All analyses will be intent to treat. A four-way analysis of variance will be used with factors shown in Table 1. The primary model will be a main effects model. Three degrees of freedom will be used to model the second factor: co-enrolling (yes-no), Omega (yes-no), and feeding (early-late). A secondary analysis will test for

the significance of two-way interactions between Albuterol, Omega and time of feeding. The primary comparison will be the main effect for albuterol.

Table 1: Factorial Design

Factor	Level
Albuterol	1. Albuterol
	2. Placebo
Co-enrollment (EDGEN-OMEGA study)	1. Not co-enrolled
	2. OMEGA + Late Feeding
	3. OMEGA + Early Feeding
	4. Placebo and Late Feeding
	5. Placebo and Early Feeding
Shock at baseline	1. Yes
	2. No

The maximum sample size will be 1000 patients. The study will be monitored using a flexible group sequential design that stops for both efficacy and futility. Since patients will be co-enrolled on two studies, the DSMB will meet at the same time for both studies. The reported confidence intervals on the treatment difference will be adjusted for the group sequential design using the method of Jennison and Turnbull.

In order to allow this flexibility we will use alpha and beta spending boundaries as described by DeMets and Ware ($z_1=2.277$, $\delta=1.663$, $z_u=2.025$, $m=4$, $\mu=3.3837$) (DeMets, 1982). Each of the treatment factors in the study will be monitored separately and could be stopped before the other stratification has stopped. Factors will be considered either as one or two sided. The OMEGA factor and the Albuterol factor are one sided while the trophic verses full feeding is two sided. One-sided factors will have an upper efficacy boundary and a lower futility boundary. Two sided factors will have a two-sided efficacy boundary and an inner wedge futility boundary that will be formed by reflecting the lower futility boundary about the abscissa. There would be no chance of futility stopping of two sided factors at the first look.

In this method of interim monitoring we specify a function $a(t)$ and $b(t)$ called the alpha and beta spending functions. The function $a(t)$ gives the amount of the p-value that will be “spent” by a given time “t” in the study, where time runs from 0 at study start to 1 when all patients have been entered. It is the probability under the null hypothesis that the trial will stop for efficacy at or before time t. The function $b(t)$ is the type II error that will be “spent” by the interim monitoring plan to allow futility stopping. It is the probability under the alternative hypothesis that the study will stop for futility at or before time t or that at the last look the efficacy boundary will not be exceeded. The reason that we use alpha and beta “spending” functions rather than p-values to stop the trial is that with two co-enrolled trials we may not be monitoring the data of both trials at 250 patient intervals.

Table 2 shows the alpha-spending boundary $a(t)$ where t is the proportion of patients accrued at that DSMB meeting. In the table we have assumed 5 meetings at $t=.10, .25, .50, .75$ and 1.0 This function $a(t)$ will be extended to a smooth function of t using a cubic spline as suggested by Tsiatis and Pampalona (Pampallona; 1994) and at each DSMB meeting the actual stopping boundary will be calculated so that the probability of stopping at or before that meeting is $a(t)$.

Similarly the futility boundary is defined by the beta-spending function $b(t)$. The number $b(t)$ is the cumulative probability that the results would be below the futility stopping boundary given the alternative hypothesis of a 2.25 day increase in VFD with a standard deviation of 10.5. At each DSMB meeting a futility stopping boundary will be calculated so that the probability of futility stopping at or before that meeting is $b(t)$ at this alternative hypothesis.

The overall one-sided significance level of the study will be 0.025 which is equivalent to a two sided $p=0.05$ significance level. Five analyses are planned after 100, 250, 500, 750 and 1000 patients. Under the assumption that there are five equally spaced interim analyses the power of the study will be 90.7%. Changes in the number or spacing of the interim analyses will have a minor effect on the power. With this design, assuming that the pattern of deaths and extubations is similar to the FACTT fluid study, there is a 82% chance that the study will show both a significant effect of VFD and a nominally positive benefit in mortality.

The DSMB will be advised to consider mortality differences in deciding whether to stop the trial. For example, they might decline to stop the trial for efficacy if the mortality difference would make the positive benefit in ventilator free days difficult to interpret and they might decline to stop the trial for futility if there is a positive mortality benefit. For example, if there was no difference in vent free days but a trend towards a survival benefit, the DSMB might continue past a futility boundary. The stopping rules have been set up so that this would not invalidate the trial if such judgments were made. The efficacy boundary has been developed without regard to the futility boundary. Thus, if the futility boundary is crossed but the trial is not stopped, the trial can still achieve a 0.025 one-sided significance level.

Table 2 on the following page shows the characteristics of this boundary if we had the interim reports described above. The second column is the nominal p-value to stop for efficacy; the third and fourth columns are the difference in VFD to stop for efficacy and futility. The next columns are the error spending functions. The type I error spending function is the probability that the upper boundary will be exceeded under the null hypothesis. The type II error spending function is the probability that the statistic will be below the lower boundary at an interim analysis or under the upper boundary at the final analysis under the alternative hypothesis. The probability of stopping for futility is given in the seventh column and the probability of stopping for efficacy in the 6th eighth column. The final column shows the confidence interval for the difference in VFD if the trial stopped for efficacy at that look, and the treatment effect just exceeded the stopping boundary.

Table 2: Stopping Boundaries

Number of patients	P-value Efficacy 2-sided	Difference Efficacy	Difference Futility	Type I Error Spending 1-sided	Type II Error Spending	Prob Stop futility	Prob Stop efficacy	Confidence interval when no difference
100	1.5 E-6	9.5		7.6 E-11	0	0	5 E-8	9.3-17.6
250	5 E-5	3.8	-0.50	2.56 E-5	0.0128	0.30	0.009	2.8-8.0
500	0.0042	1.9	0.14	0.0021	0.0232	0.31	0.31	.8-4.5
750	0.0194	1.3	0.35	0.0104	0.0287	0.17	0.41	.3-3.2
1000	0.0429	0.95	0.46	0.0250	0.0923	0.09	0.18	0.0-2.6

Secondary Endpoints

Mortality

Mortality will be compared at interim data analyses using Kaplan Meier estimates at 60 days and their associated standard errors. This analysis will be stratified as above and a test for interaction of treatment with strata will be presented. At the end of the study sixty-day mortality will be compared using a Mantel-Haenzel test as long as all patients can be followed. If not the method used for the interim analyses will be used.

Other Endpoints

The number of ICU-free, Organ-Failure Free, and days from first weaning readiness will be analyzed in the same manner as is described above for the primary endpoint. Subset analysis defined in the secondary analyses section will use an analysis of variance. First we will check for interactions and then, if significant, analysis will be performed for each of the specified subsets. In addition we will test for interactions between treatment and gender and race as per NIH guidelines (<http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>).

Changes in plasma and mini-BAL levels of IL-6, IL-8, and protein will be compared in two analyses. An analysis of covariance will test for a treatment effect on the day 3 value of these variables using the day 0 value as a covariate. In addition a multivariate analysis of variance will test for a baseline difference between day 3 and day 0. Table 3 illustrates the detectable differences for endpoints, assuming 1000 patients enrolled, 90% power, and a two-sided alpha-level of 0.05.

Table 3: Detectable Differences for Secondary Endpoints

Variable	Incidence or Mean	Standard Deviation	Detectable Difference
PaO ₂ / FiO ₂	155	73	15
ICU free days	13.4 days	12.6 days	2.6 days
Shock free days	19.1 days	4.93 days	2.23 days
Plasma IL-6 (pg/ml)	1252	862	177
Plasma IL-8 (pg/ml)	149	93	19
28-day hospital mortality	22%		8.2%
90 day hospital mortality	25.4%		8.6%

Changes in physiologic lung indices on days 1-7 will be compared using a multivariate analysis of variance.

5.1. Phase II Safety Assessment

The first 100 patients will be randomized to placebo or 5.0 mg of albuterol. The protocol stipulates that the dose of 5.0 mg will be reduced in half if heart rate exceeds specified limits. The steering committee will review the safety data on these patients and will decide whether the active treatment will be 2.5 mg or 5.0 mg based on the number of patients who require dose reductions (see below) and the overall safety profile. The Steering Committee will not be given the outcome data (all study endpoints). The Steering Committee decision will be independently reviewed by the DSMB, as described in Appendix G. In addition, the steering committee and the DSMB will be immediately notified of any severe unexpected adverse event (Appendix C).

Dose decisions will be based on the occurrence of severe adverse events to the 5.0 mg treatment and the frequency of dose reductions due to tachycardia. The decision about whether the frequency of adverse events is too high will not have formal evaluation criteria. However, the DSMB will be provided with summary statistics of baseline and on-study vital signs and laboratory values as well as tabulations of all the studies endpoints. All episodes of hypokalemia (less than 2.5 mEq/l) detected as part of clinical care will be compared between groups. With 50 patients in the 5.0 mg group we will have over a 90% chance of seeing at least one occurrence of any event that would occur with a frequency of over 4.6 percent.

The protocol specifies a dose reduction for patients who develop tachycardia when receiving 5 mg doses. This is not necessarily a severe adverse event but if it occurs in a large number of patients we will decrease the starting dose to 2.5 mg. We will make this decision on the basis of the first 50 patients randomized to the 5 mg dose. The guidelines for this decision are as follows. If more than 15 out of the first 50 patients (30 % of the subjects) require a permanent dose reduction due to heart rate increases then all subsequent patients will start at a 2.5 mg dose. Using this guideline there is a 95% chance that we will reduce the dose to 2.5 mg if the true rate of dose reductions is as high as 40% and there is only a 6% chance that we would reduce the dose if the true rate of dose reductions is 20%. If the analyses of an increase in heart rate are conducted with a different number of patients the cut-off value of 15 will be modified to have close to a 5% chance of rejecting a 20% rate and a 95% chance of rejecting a 40% rate. We do not expect to see many occurrences of permanent dose reduction on the placebo arm, as this would require a spontaneous heart rate increase on two separate occasions. The DSMB will be instructed to modify this rule if permanent dose reductions are common on placebo.

The phase II data will also be analyzed for the frequency of off-protocol use of albuterol. Any patient with more than 30 mg off protocol will be considered a “too-frequently” off protocol subject. If this exceeds 10 % of enrolled patients in phase 2, then the steering committee will evaluate how this can be decreased to less than 5 percent of patients.

5.1.1 Number of Subjects in Phase II

The CCC will prepare a Phase II analysis of the first 100-120 patients, and the steering committee and DSMB review will occur while the study continues. If the steering committee and DSMB recommend that the study proceed to Phase III, as summarized in section 5.1.2 below, and the NHLBI accepts these decisions, then the IRBs and the FDA will be notified and study will continue to Phase III as outlined in this protocol.

5.1.2 Summary of Guidelines for Steering Committee and DSMB Assessment for Progression to Phase III

A decision to proceed to Phase III using the 5 mg dose of Albuterol may be made if all of the following occur during the Phase II assessment of 80-120 subjects:

- 1) The rate of dose reduction for tachycardia in the albuterol group is less than 30%,
AND
- 2) No clinically significant differences between albuterol and placebo subjects in the rates of:

- a. Atrial arrhythmias
- b. Ventricular arrhythmias
- c. Hypokalemia
- d. All adverse events

AND

- 3) No indication of harm in the evaluation of all the primary and secondary endpoints (DSMB only)

AND

- 4) Rates of off-protocol albuterol use is less than 10%

A decision to proceed to Phase III using the 2.5 mg dose of Albuterol may be made if all of the following occur:

- 1) The rate of dose reduction for tachycardia in the albuterol group exceeds 30 % AND
- 2) Conditions 2 through 4 above are met.

These are guidelines for decision-making. The steering committee and DSMB may elect to terminate the study based on the nature and seriousness of infrequent adverse events (eg. ventricular fibrillation) even if the frequency of such events is not statistically different between groups.

6. Data Collection and Adverse Event Reporting

6.1. Data Collection

The research coordinator will be responsible for maintaining a database using a custom designed web-based database application. Data will be stored on a secure server at the Clinical Coordinating Center.

6.2. Adverse Events

Investigators will determine daily if any clinical adverse experiences occur during the period from enrollment to 72 hours after last dose of study drug.

6.2.1. Reportable Adverse Events

For this trial, a *reportable adverse event* is defined as:

1. Any clinically important untoward medical occurrence in a patient receiving study drug or undergoing study procedures which is different from what is expected in the clinical course of a patient with ALI, *or*:
2. Any important, untoward medical occurrence that is thought to be associated with study drug or procedures, regardless of the events “expectedness” for the course of a patient

with ALI. For this study, events considered “contraindications to albuterol” (Appendix A.8) that emerge during the study will also be reported as adverse events.

The investigator will evaluate any changes in laboratory values and physical signs and will determine if the change is clinically important and different from what is expected in the clinical course patients with ALI. *Expected events for ALI* are untoward clinical occurrences that are perceived by the investigator to occur with reasonable frequency in the day to day care of patients with ALI treated in an intensive care unit with mechanical ventilation. Examples of adverse events that are expected in the course of ALI include transient hypoxemia, agitation, delirium, nosocomial infections, intolerance of gastric feeding, skin breakdown, and gastrointestinal bleeding. Such events, which are often the focus of prevention efforts as part of usual ICU care, will not be considered reportable adverse events unless the event is considered by the investigator to be associated with the study drug or procedures, or unexpectedly severe or frequent for an individual patient with ALI. Examples of unexpectedly frequent adverse events would be repeated episodes of unexplained hypoxemia, in contrast to an isolated episode of transient hypoxemia (e.g. SpO₂ ~85%), particularly if related to positioning of suctioning. This latter event would not be considered unexpected by nature, severity or frequency.

An event will be considered to be study-related if the event follows a reasonable temporal sequence from the study drug/procedure and could readily have been produced by the study drug/procedure. An event will be considered to be *unexpected for study drug* if it is not identified in the package insert, or is unexpectedly severe or more frequent than events described in the package insert.

6.2.2. Clinical Outcomes

Events leading to death and organ failure are being systematically captured in the case report forms and will be systematically analyzed per protocol as part of the safety and efficacy analysis. The following clinical outcomes will not be considered to be adverse events *if the investigator feels the outcomes were not study drug or procedure-related*:

1. Death
2. Respiratory: worsening hypoxia, prolonged need for ventilation, hypoxemia, hypercarbia, respiratory acidosis, high airway pressures.
3. Circulatory: circulatory shock requiring vasopressors.
4. Hepatic: hepatic injury that leads to a rising bilirubin.
5. Renal: rising creatinine.
6. Coagulopathy: falling platelet count.

6.2.3. Definition of Serious Adverse Events

For this study, a serious adverse event is any untoward clinical event that is not included as a clinical outcome (6.2.2), and is thought by the investigator to be study-related, and is:

1. Fatal or immediately life threatening
2. Permanently disabling or severely incapacitating.
3. Requires or prolongs inpatient hospitalization.

4. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the serious outcomes listed above.

Contraindications to albuterol (**Appendix A.8**) that occur after study entry will also be considered adverse events.

6.2.4. Adverse Events Reporting Timeline

If clinically important and unexpected adverse experiences or clinically important study-related adverse experiences occur they will be recorded on the adverse event case report form. Investigators will report all serious, and unexpected, and study-related adverse events, as defined in Appendix C, to the Clinical Coordinating Center within 24 hours. The local Institutional Review Board must also be notified 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. The Medical Monitor (an Intensivist Physician working at the CCC) will work with the reporting investigators to prepare a detailed written summary of serious, unexpected, and treatment related adverse events and will compare and contrast the event with prior events.

The Clinical Coordinating Center will report all serious, unexpected, and study-related adverse events to the NHLBI within 24 hours and the FDA, by fax or telephone, within 7 calendar days of the coordinating center being notified of the event. A written report will be sent to the FDA and the DSMB within 15 calendar days and these reports will be sent to investigators for submission to their respective Institutional Review Boards. The DSMB will also review all adverse events during scheduled interim analyses. The Clinical Coordinating Center will distribute the written summary of the DSMB's periodic review of adverse events to investigators for submission to their respective Institutional Review Boards in accordance with NIH guidelines.

6.2.5. Adverse Event Summary Reports

NHLBI Project Officer will prepare a summary report of the DSMB's findings for both *ad hoc* reviews of serious unexpected adverse events and after reviews of aggregate adverse event data as part of the protocol-specified interim analyses (Section 5). The CCC will send these reports attached to the adverse event narrative (for *ad hoc* reports) or attached to a tabulation of all adverse events (following protocol specified interim analyses or annual adverse event summaries) to Principal Investigators. The CCC will require written confirmation that these reports have been forwarded to local Institutional Review Boards. The CCC will forward this written confirmation to the NHLBI. These adverse event summaries will also be sent to FDA as they occur or as part of the annual IND Safety report in accordance with applicable Federal Regulations.

These adverse reporting standards are to be followed regardless of applicable regulatory requirements that may be less stringent.

7. Site Monitoring

Site visits will be performed on a regular basis by the Clinical Coordinating Center to ensure that all regulatory requirements are being met and to monitor the quality of the data collected. Records of all IRB approvals and critical documents will be reviewed and a random sample of patient charts will be examined to evaluate the accuracy of the data entered into the database.

8. Risk/Benefits

8.1. Risk Assessment

Aerosolized albuterol in mechanically ventilated patients with acute respiratory failure from asthma or chronic airways obstruction is currently part of usual clinical care. Because of substantial deposition of aerosolized albuterol in the ventilator circuits (greater than 80%), higher doses are recommended for mechanically ventilated patients than those recommended for spontaneously breathing patients using a hand-held nebulizer (MacIntyre, 2002b, Dhand, 1997). Doses customarily are 2.5 mg-5.0 mg of albuterol by aerosol, with some reports of up to 10 mg per hour of continuous albuterol being well tolerated in mechanically ventilated patients with severe asthma. Recommended dose frequencies vary from continuous nebulization to every 6 hours for patients with milder exacerbations of COPD (MacIntyre, 2001). See additional discussion of these issues in the background. It is possible that one treatment arm may lead to more deaths. Mortality is a secondary outcome and it will be monitored during the course of the study.

Modest systemic absorption of the aerosol dose delivered to the lung and beta-2 selectivity minimizes the systemic cardiovascular side effects, such as tachycardia. As with all sympathomimetic amines, cardiac arrhythmias, hypertension, myocardial ischemia may occur but are infrequent (see background). Large doses have been reported to aggravate diabetic ketoacidosis and hyperthyroidism and may cause hypokalemia. Currently, aerosolized beta-2 agonists are not FDA approved for treatment for patients with ARDS and their safety is unknown in this clinical setting.

8.2. Minimization of Risks

Federal regulations at 45 CFR 46.111(a)(1) requires that risks to subjects are minimized by using procedures which are consistent with sound research design. There are several elements of study design inherent in the present protocol that meets this human subject protection requirement. First, several of the exclusion criteria prohibit participation of patients who might be at increased risk from the effects of the beta₂-agonists. These include individuals with acute myocardial infarction within 30 days or acute coronary syndrome, congestive heart failure, and excessive heart rates. Furthermore, women who are pregnant are excluded due to concerns with uterine contractions from the effects of beta₂-agonists.

Individuals with contraindications to albuterol are also excluded. These include previous hypersensitivity reactions to albuterol or prior episodes of paradoxical bronchospasm, arrhythmias such as atrial fibrillation with a rapid ventricular response (greater than 140/min), persistent and or severe hypokalemia, thyrotoxicosis, uncontrolled diabetes mellitus, and uncontrolled systemic hypertension. In addition, patients will be monitored as part of usual clinical care for the development of these contraindications.

While these contraindications are considered relative contraindications in clinical care, for this trial they will be absolute contraindications and if treatment emergent will be reported as adverse events.

Patients with ALI and ARDS may also have underlying conditions that would benefit from aerosolized beta agonists as part of clinical care, such as asthma or chronic obstructive pulmonary disease, in which placebo aerosol would not be ethical. To exclude such patients, individuals receiving daily inhaled beta agonists or corticosteroids or oral leukotriene modifiers for acute or chronic obstructive airway disease will be excluded from participation.

Second, there are provisions in the protocol for either reduction of the study drug dose or discontinuation of the study drug for excessive tachycardia, arrhythmias, or hypokalemia. Study drug will be held for hypokalemia until potassium supplementation in accordance with local ICU practice achieves a potassium level of 3.0 mEq/L or greater (see section 3.1.6).

Third, administration of beta₂-agonists is permitted for those subjects who develop bronchospasm during the study period. Specifically, patients with previously undiagnosed airway reactivity may develop clinical bronchospasm during participation in the trial. This may manifest by wheezing on physical examination, rising peak airway pressures, evidence for air trapping, or a widening difference between plateau airway pressures and peak airway pressures. Retained secretions or a malpositioned/partially occluded endotracheal tube are potential causes for these findings and are evaluated for and treated as part of routine ICU care. If the attending physician elects to begin an aerosol bronchodilator during study days 0-10, then ipratropium would be an option per local ICU protocol. If the attending physician wishes to use an aerosol beta agonist (albuterol, salmeterol, metaproterenol, terbutaline, epinephrine, or others) then study drug would be discontinued. If the attending physician discontinues a non-study aerosol beta agonist because of lack of efficacy within 24 hours, reinstatement of study drug would be permitted if the patient was still receiving mechanical ventilation on study day 10 or less, or was within 24 hours of extubation on study day 10 or less.

8.3. Potential Benefits

Study subjects may or may not receive any direct benefits from their participation in this study. Potential benefits from the administration of beta₂-agonists include decreased requirement for ventilatory support, decrease days spent in the ICU, and increased organ failure free days and enhanced survival. Finally, there are potential benefits to society, as the discovery of agents that can reduce the substantial mortality and morbidity of ALI and ARDS would enhance the health of society.

8.4. Risks in Relation to Anticipated Benefits

Federal regulations at 45 CFR 46.111 (a)(2) require that “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. Also, the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting.

Procedures: Blood draws and mini-BAL. The risks associated with these common clinical practices are small, however, the knowledge gained in furthering our understanding of the pathophysiology and potentially leading to better and targeted therapy may be substantial.

Treatments: The treatment arms are consistent with clinical practice. There is potential for benefit to society and individual patients should one treatment arm prove to be of benefit. Should one treatment arm, again consistent with clinical practices, prove to be harmful, the benefit will be in avoiding such therapies for future patients with ALI/ARDS.

9. Human Subjects

9.1. Selection of Subjects

9.1.1. Equitable Selection of Subjects

Each study participant or a legally authorized representative must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The ICUs will be screened to determine if any patient meets the inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests or procedures will be performed as part of the screening process. If any subjects meet criteria for study enrollment, then the attending physician will be asked for permission to approach the patient or his/her surrogate for informed consent.

Justifications of exclusion criteria are given in Section 1.4.3. These exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

9.1.2. Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of a type of treatment for patients with acute lung injury and acute respiratory distress syndrome. Due to the nature of these illnesses, most of these patients will have impairment decision-making capabilities. Hence, it will be impossible to perform this research only on subjects who retain decision-making

capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

9.2. Informed Consent

Federal regulations at 45 CFR 46.111(a)(5) require that informed consent will be sought from each prospective subject or the subject's legally authorized representative. The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, and answering any questions the patient may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's willingness to continue his or her participation in the trial. The consentor will make every effort to minimize coercion. All study participants or their surrogates will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study agent.

9.3. Continuing Consent

For subjects for whom consent was initially obtained from a surrogate, but who subsequently regains decision-making capacity, all sites will obtain formal consent for continuing participation, inclusive of continuance of data acquisition. The initial consent form signed by the surrogate should reflect that such consent will be obtained.

9.4. Justification of Surrogate Consent

9.4.1. Identification of Surrogates

Many of the patients approached for participation in this research protocol will invariably have limitations of decision-making abilities due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's next of kin.

Regarding proxy consent, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research...unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46.102 (c) a legally authorized representative (LAR) as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." OHRP defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the surrogate to provide consent for subject participation in the research.

Interpretation of “applicable law” is therefore state specific and hence, will be left to the discretion of the individual IRBs of the respective clinical centers involved in the ARDSNet.

According to a previous President’s Bioethics Committee (National Bioethics Advisory Committee), an investigator should accept as an LAR...a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision-making under the law of the state where the research takes place (NBAC, 1998). Finally, OHRP has opined in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the “procedures” involved in the research study (OHRP, 2002).

9.4.2. Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protections. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and Research Ethics Commission have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting (Dresser, 1999). Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians’ document allows surrogates to consent to research involving incapable subjects only “if the net additional risks of participation are not substantially greater than the risks of standard treatment.” (American College of Physicians, 1989). Finally, the National Bioethics Advisory Committee (NBAC) stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that...the potential subject’s LAR gives permission...” (NBAC, 1998)

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is *similar* to that available in the clinical setting, with the exception of the additional blood draws and mini-BAL.

9.5. Additional Safeguards for Vulnerable Subjects

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that additional safeguards be included to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) assessment of the potential subject’s capacity to provide informed consent, b) requirement for subject’s assent, c) the availability of the LAR to monitor the subject’s subsequent participation and withdrawal from the study; d) augmented consent processes; and e) independent monitoring of the subject’s participation in the study, e.g., to ensure that the risk-potential benefit ratios continue to be acceptable throughout the course of the study. The specific nature of the additional safeguards will be left to the discretion of the individual IRBs.

Minors (13-18 years old)

This study will enroll minors between the ages of 13-18. As this is a vulnerable population the consent form will include a section for obtaining assent for the minor coupled with permission from a parent for both study enrollment and continuation. The assent for continuation will be invoked when surrogate consent is obtained initially (subject not able to self enroll due to illness). In accordance to the decision matrix provided in 45 CFR 46, Children as subjects of research (<http://www.hhs.gov/ohrp/panels/407-01pnl/riskcat.htm>) we have designed the IRB approved project assent form to require one parental permission signature, as the study is greater than minimal risk with the potential for direct benefit to the subject (46.405).

9.6. Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. The coded number will be generated at random by a computer, and only the study investigators will have access to the codes. All records will be kept in a locked, password protected computer. The case report forms will be maintained in a locked cabinet inside a locked office. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the National Heart, Lung, and Blood Institute, and the ARDS Clinical Coordinating Center.

Appendices

A. Exclusion Definitions and Clarifications

A.1 Malignant and Irreversible Conditions

1. Poorly controlled neoplasms.
2. Known HIV positive with known end stage processes (i.e. progressive multifocal leukoencephalopathy, systemic mycobacterium avium infection) with known CD4 count less than 50.
3. Prior cardiac arrest requiring CPR without fully demonstrated neurologic recovery.
4. New York Heart Association Class IV subjects (defined as subjects who have cardiac disease resulting in inability to carry out physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased).
5. Chronic respiratory condition making patient respirator dependent.

A.2 Child-Pugh Score

<u>Points</u>	<u>Class</u>
5-6	A
7-9	B
= 10	C

Measurement	Numerical Score for Increasing Abnormality		
	1	2	3
Ascites	None	Present	Tense
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dl)	Less than 2	2-3	Greater than 3
Albumin (g/L)	Greater than 35	28-35	Less than 28
Prothrombin time (sec. Prolonged)	1-4	4-10	Greater than 10

A.3 Neuromuscular Disease Impairing the Ability to Ventilate Spontaneously

1. Amyotrophic lateral sclerosis
2. Guillain-Barré Syndrome
3. Myasthenia gravis
4. Upper spinal cord injury at level C5 or above
5. Chest wall deformity resulting in severe exercise restriction (unable to climb stairs or perform household duties), secondary polycythemia, or respirator dependence

A.4 Severe Chronic Respiratory Disease

1. FEV₁ less than 20 ml/kg PBW (e.g. 1.4 L for a 70 kg person), or
2. FEV₁/VC less than 50% predicted, or
3. Chronic hypercapnia (PaCO₂ greater than 45 mmHg) and/or chronic hypoxemia (PaO₂ less than 55 mmHg) on F_IO₂ = 0.21, or
4. Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
5. Hospitalization within the past six months for respiratory failure (PaCO₂ greater than 50 mmHg or PaO₂ less than 55 mmHg or O₂-Sat < 88% on FiO₂ = .21).
6. 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 greater than 40 mmHg), or respirator dependency.

A.5 Congestive Heart Failure

1. Left ventricular ejection fraction of less than 40%
2. Hospitalization within the past six months for congestive heart failure
3. History of congestive heart failure with New York Heart Association Class IV activity level.

A.6 Acute Myocardial Infarction Within 30 Days

Troponin (I or T) may be increased in patients with sepsis in the absence of an acute MI or acute coronary syndrome from coronary artery disease. If, in the judgment of the clinical team a *septic* patient with elevated troponin levels has *no other indication* of an MI, the patient may still be eligible.

A.7 Age Exclusion for Tachycardia

Patients with a heart rate greater than 85% maximal predicted HR (MHR85) as calculated by: $MHR85 = 85\% \times (220 - \text{Age})$ will be excluded from participation in this trial (Exclusion A7).

However, potential subjects who are excluded from enrollment at initial screening only because of Exclusion A.7 can be reassessed hourly. If Exclusion A.7 is absent on two separate subsequent observations separated by one hour, the subject should then be considered eligible for enrollment if they are still within the 48-hour enrollment window (as described on page 27).

Dose Interruptions and Adjustment for Tachycardia

Hold Parameters for Heart Rate Prior to and During Study Drug Aerosolization

Heart rate will be monitored continuously by a bedside monitor.
MHR=220-age

1) Do not give scheduled study drug dose if sustained pretreatment HR is greater than either 140 or 85% of MHR whichever is lower. If heart rate exceeds this threshold reassess heart rate at the next scheduled treatment time.

2) If during nebulization HR is greater than either 140 or 85% of MHR whichever is lower, stop the current treatment and reassess heart rate at the next scheduled treatment time.

Thus, if any of the above three heart rate conditions are met, the aerosol will be held and the patient will be reassessed for suitability to receive study drug again in four hours.

Because fluctuations in heart rate during critical illness may be multifactorial (pain, general stress response, alterations in acid base status), the ICU team will evaluate the patient and a cause for tachycardia other than study drug will be sought and if identified, treated. The next scheduled aerosolization of the **full dose** of study drug will then be given and if the heart rate increases to the above thresholds a second time, the aerosol will be held and subsequent study drug doses will be reduced to 0.5 ml (2.5 mg of albuterol or saline) with 2.5 ml diluent (referred to subsequently as **reduced dose**). If heart rate increases to the above thresholds on two consecutive **reduced** study drug doses, study drug will be held for 24 hours and restarted at the reduced dose. A subsequent increase in heart rate to the above thresholds will result in the study drug being held for another 24 hours and restarted at the **reduced** dose. Any subsequent increases in heart rate to the above thresholds will result in discontinuation of study drug for the duration of the study. With this approach, a patient may not tolerate study drug in the first 48 hours, even at half the initial dose, but then still be able to receive the study drug from day 3-10.

To facilitate implementation of this rule, coordinators will access a web site loaded with a simple calculator for determining MHR85. This value will be recorded on the bedside study data sheet and will be referred to as guidance for all study medication administration events.

A.8 Contraindications to Albuterol

Patients with these conditions are excluded from participation in the trial. These complications, should they develop while on-study, will be considered adverse events regardless of the investigators assessment as to the relationship of these events to the study drug and regardless of the investigators assessment as to the “expectedness” of the event for a patient with ALI. If the investigator judges the event to be serious and unexpectedly severe or frequent and treatment related (as defined in 6.2.3) then the CCC must be notified within 24 hours of the identification the event by study personnel (see Appendix C for adverse event reporting timelines).

1. Hypersensitivity to albuterol: Albuterol is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components (benzalkonium chloride, sulfuric acid; albuterol solution as Proventil (Schering) is sulfite free).
2. Paradoxical bronchospasm: Albuterol solution may cause paradoxical bronchospasm, which may be life threatening.

3. Arrhythmias: Albuterol, like all other beta agonists, can produce clinically significant cardiovascular effects including tachycardia and elevated blood pressure and, for this trial, is contraindicated in patients with acute coronary syndromes, cardiac arrhythmias, uncontrolled hypertension, or a resting heart rate greater than 140 beats per minute or MHR 85%, whichever is lower. Patients should not be enrolled if they have any episodes of PVCs greater than 5/min in the 4 hours prior to randomization. If they later have a 4-hour period without more than 5 PVC/min and are still in the 48-hour window, they can still be enrolled.
4. Hypokalemia: All beta-agonists may produce hypokalemia due to intracellular shifts of potassium. Hypokalemia is usually transient and does not require supplementations. Patients with serum potassium values, detected as part of routine clinical care, less than or equal to 3.0 mEq/L will be excluded or will have study drug held until K level is great than 3.0. Any potassium levels less than or equal to 2.5 mEq/L must be reported as expedited adverse events to the CCC within 24 hours of detection by study personnel.
5. Monoamine oxidase inhibitors: Patients receiving monoamine oxidase inhibitors may experience severe hypertension following albuterol exposure and are excluded. [Examples: Carbox (selegiline), Marplan (isocarboxazid), Matulane (procarbazine), Nardil (phenelzine), Parnate (tranylcypromine)]
6. Pregnancy: Albuterol may interfere with uterine contraction and pregnant patients are excluded.
7. Hyperthyroidism: Albuterol may worsen symptoms of hyperthyroidism and patients with clinically diagnosed hyperthyroidism are excluded.
8. Diabetic ketoacidosis or uncontrolled diabetes: Albuterol may worsen glycemic control and patients with clinically diagnosed diabetic ketoacidosis or otherwise uncontrolled diabetes will not be entered into the trial. Diabetes management during the trial will be part of usual care.
9. Uncontrolled hypertension

B. Schedule of Events

Measurement/Event	Day 0	1	2	3	4	5	6	7	8	9	10	11	12	14	21	28	60
Demographics, History & Physical, height, weight ∞	X																
Etiology of ARDS, site of sepsis if septic etiology	X																
APACHE III score ^C	X																
HCG (in females)	X																
Vital Signs (HR, SBP, DBP, Temp °C) *	X	X	X	X	X	X	X	X	X	X	X						
Central Venous Pressure *	A	A	A	A	A	A	A	A	A	A	A						
Fluids (In and Out)*	X	X	X	X	X	X	X	X									
Brussels Score ~ ^B	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glasgow Coma Scale	X							X								X**	
Ventilator Parameters (including FIO ₂) *#	X	X	X	X	X								X		X	X	
Arterial Blood Gases and SpO ₂	X	A	A	A	A			A					A		A	A	
Serum glucose, Hgb, Na+, K+, HCO ₃	X	A	A	A	A	A	A	A	A	A	A	A	A				
Creatinine, Platelets, Bilirubin, BUN, Hct, WBC	X																
CXR (quadrants with infiltrates for lung injury score)		A	A	A	A	A	A	A	A	A	A						
Record Vasopressors, and Inotropes	X	X	X	X	X	X	X	X	X	X	X						
Record Aerosol Beta Agonists		X	X	X	X	X	X	X	X	X	X						
Record Sedatives, narcotics, pressors *	X	X	X	X	X	X	X	X	X	X	X	X	X				
Plasma for EpinephrineΦ	X	X															
Plasma Albuterol LevelΦ		X															
Plasma for Cytokines IL-6, IL-8	X			X													
Whole blood for DNA	X																
INR, PT, platelet count (prior to mini-BAL)	X			X													
Mini-BAL for IL-6, IL-8, SP-D, VWF, & protein *	X			X													
Urine leukotriene B and isoprostane metabolites	X			X													
Pulmonary dead-space measurement***	X	X	X	X				X									
Study Drug Administration Record *	X	X	X	X	X	X	X	X	X	X	X						
Vital Status § and a/fib history κ																X	X

X Required

A When available

** On day 28 or on the discharge date

* Data gathered at times indicated or until patient achieves extubation plus 48 hrs of unassisted breathing, whichever is sooner

∞ AUDIT survey should be completed by subject or surrogate at baseline. It should NOT be completed for subjects less than 18 years of age.

§ Measure at 90 days and 12 months as part of Long-term outcome.

κ Complete once at ICU discharge (follow through day 28 or ICU d/c).

Measure during the reference period (0600-1000); other values may be obtained closest to 8 am on the specified calendar date.

+ Data gathered until 48 hours after the last dose of study drugs.

Φ Phase II, i.e. first 60-105 patients

*** At selected sites

~ Data gathered on day 0-28 or until d/c from study hospital

^B Records clinically available creatinine, platelets, bilirubin, SBP and vasopressor use

^C Labs not available in the 24 hours before randomization must be obtained

C. Adverse Event Reporting Procedures

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. The Principal Investigator will evaluate all adverse events. The Study Coordinator must view patient records for possible adverse events throughout the study period. All adverse events occurring within the study period must be reported in the participants' case report forms.

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

2. Definitions 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. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This definition does not include a reaction that, had it occurred in a 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* event is any experience not identified by the type, severity, or frequency in the current study protocol or an event that is unexpected in the course of treatment for ALI or ARDS.

Adverse events will be considered to be study-related if the event follows a reasonable temporal sequence from a study procedure and could readily have been produced by the study procedure.

Organ failures related to ALI or ARDS or the patient's underlying condition should not be reported as adverse events since they are systematically captured by the protocol data collection.

D. Blood for Genetic Testing

Portions of the blood specimens as specified in this protocol will be used for genetic analyses either for beta-receptor polymorphisms as part of an ancillary study, or for future genetic studies of ARDS that are presently undefined. ALI is a complex inflammatory condition of the lungs, and many of the inflammatory pathways thought to be involved in lung injury are associated with genetic polymorphisms. It is likely that there are, as yet undetermined, important gene/environment interactions that impact on clinical outcome. Thus it is important to collect and store DNA from large, carefully described cohorts of patients with ALI to facilitate discovery in this field with the aim to better understand the pathogenesis of ARDS and how treatment may be tailored to individual patient needs.

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 as follows: 1) consent for genetic studies related to ARDS, or; 2) consent for future studies not necessarily related to ARDS. The level of 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. All patients who recover decision-making capacity will be approached for written re-consent for genetic testing.

Two 7.5 ml EDTA plastic monovette tubes will be used to collect up to 10 ml of blood on each patient with consent for genetic testing. Samples will be labeled with pre-printed label with the subjects ARDSNet study number. DNA extraction will be done centrally.

Following extraction, DNA will be sent to a central repository to be stored (as described below). DNA will first be stored at the extraction laboratory for seven years and then shipped to the central repository. Samples will be identified by a random number during shipment, extraction, and storage in the central repository. In the future, when approved studies for genetic testing are received at the CCC, the CCC will identify samples that have the necessary level of informed consent for genetic testing. The CCC will then instruct the repository to prepare the appropriate samples for shipment. The key relating the ARDSNet study number to the new specimen number will be kept at the CCC in a locked file. The CCC does not record or store unique patient identifiers (such as initials, date of birth, hospital record numbers, addresses, phone numbers, etc.) in the database. All data released by the CCC for genetic studies be linked to the specimen but will be de-identified. The link (key) between the de-identified database and the patient will be removed two years after the primary publication.

Should patients or surrogates revoke their consent for genetic testing, the clinical sites will notify the CCC. The CCC will then contact the repository and request that all samples collected for genetic analysis for that patient be destroyed. Confirmation of destruction of samples will be sent to the CCC and forwarded to the clinical site.

E. De-identified Data Elements for Screened, Non-Enrolled Subjects

- Was onset of ALI acute?
- Did frontal CXR show bilateral infiltrates consistent with pulmonary edema?
- Number of quadrants with opacities?
- Is patient intubated?
- PaO₂
- FiO₂
- Was there evidence of left atrial hypertension?
- Month of the year that patient met screening criteria (1-12).
- Gender
- Ethnicity
- Age (if age greater than 89, 89 will be entered for age)
- Patient location (e.g. MICU, SICU, etc.) and if regularly screened
- Reason(s) patient excluded from study.
- If not excluded, not enrolled, why?
- Lung injury category (e.g. sepsis, pneumonia)
- If lung injury category=sepsis, site of infection

F. Acceptable Aerosol Devices

A small volume jet nebulizer that can be adapted to a mechanical ventilator circuit and be powered by an 8 L/min gas flow is required. Particle size for most efficient aerosol delivery during mechanical ventilation is a mass median aerodynamic diameter (MMAD) less than 2 microns,¹ but at a minimum should be at least less than or equal to 3 microns.⁹ Devices should thus have a MMAD of less than or equal to 3 microns and have a 4 ml nebulization time of less than 13 minutes. Residual volume should be less than 0.5 ml. Currently we have identified 2 nebulizers that meet these specifications. These two nebulizers are as follows: Micromist (Hudson), Mistymax 10 (Cardinal).

F1 Citations for appendix F

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G. Data and Safety Monitoring Board

The principal role of the DSMB is to regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations, as appropriate, to the NHLBI with respect to:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of early attainment of study objectives, safety concerns, or inadequate performance
- Desirability of proceeding to the full-scale trial at the completion of the Phase II phase
- Possible modifications in the clinical trial protocol
- The performance of individual centers

The NHLBI ARDS Network DSMB is appointed by the Director, NHLBI. The DSMB reviews all new protocols for safety following review by an independent NHLBI Protocol Review Committee. The DSMB will consist of members with expertise in acute lung injury, biostatistics, ethics, and clinical trials. Ad hoc members have been appointed with particular expertise where necessary. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The DSMB will review data prepared by the CCC. Decisions regarding issues such as stopping guidelines or whether the DSMB may at times remain blinded to study group identity will be made jointly by the DSMB members and the NHLBI representatives. The Principal Investigator and the Medical Monitor of the CCC will be responsible for the preparation of DSMB and adverse event reports and may review unblinded data. DSMB meetings will be scheduled by the NHLBI at intervals as described in section 5.0, and the DSMB will review the protocol during its first meeting. When appropriate, conference calls may be held in place of face-to-face meetings.

Recommendations to end, modify, or continue a trial will be prepared by the DSMB executive secretary for review by Director, NHLBI, no more than two working days after a DSMB meeting. Recommendations for major changes, such as stopping, will be communicated immediately, and followed by a written summary. The NHLBI will act on recommendations expeditiously; the NHLBI Project Officer or Program Scientist will communicate the recommendations promptly to the ARDS Network Steering Committee and the CCC with instructions for reporting to local IRBs when appropriate. The executive secretary of the DSMB will be responsible for preparing the minutes for each meeting or conference call. Details of the NHLBI policies regarding DSMBs can be found at the following URL:
http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm

The ARDS Network Steering Committee is comprised of the Principal Investigators and Co-investigators of all the Clinical sites, the CCC, and the NHLBI Project Officer who represents the NHLBI. All sites and the CCC have one vote, which is advisory to the NHLBI.

H. Mini-Bronchoalveolar Lavage Procedure

The mini-BAL procedure involves blind specimen sampling from distal airspaces. Specimens are obtained with the Combicath™ (Plastimed) catheter that is commonly used for the diagnosis of ventilator-associated pneumonia. The catheter is introduced from its protective sheath into the endotracheal tube through a standard bronchoscopy adapter, and then gently advanced into the lungs until it becomes wedged in a distal airway. The catheter then is withdrawn approximately 3 cm to allow room for the inner catheter to be advanced into the distal airway. This is accomplished by removing the white protective spacer and gently advancing the inner catheter to its full length and securing it to the outside catheter by slightly twisting it into the outside catheter. Then, two 30-mL syringes containing 20 mL normal saline and a 5mL air bolus are injected rapidly into the lungs. Once the air bolus clears the second syringe, gentle aspiration is applied to the syringe for approximately 10 seconds to retrieve as much of the instilled fluid as possible (usually 5-10 ml). When completed, the catheter is removed from the endotracheal tube. The recovered aspirated samples are then emptied into a standard screw-top specimen container used for BAL samples. If the clinical condition warrants it, 1 ml can be deposited into a sterile container to be sent to the microbiology laboratory for culture.

Note: The mini-BAL procedure can be done with either one or two clinicians but it is easier to do (and typically more effective) when two clinicians are involved: one to advance, wedge, and manipulate the Combicath and the other to instill and aspirate the lavage. The patient should be pre-oxygenated on an FiO_2 of 1.0 for 10 minutes prior to the procedure and routine endotracheal suctioning should be done first to remove sputum from the airways.

After the mini-BAL, routine suction should be repeated to remove any excess BAL fluid that may be present in the airways. Assess patient's oxygenation and ventilatory status and return patient to their baseline FiO_2 when clinically indicated, usually within 5-10 minutes. The ventilator circuit should be returned to its original configuration by replacing the bronchoscopy swivel adapter with a clean adapter that was originally present in the circuit.

The mini-BAL should NOT be performed under the following circumstances:

1. FiO_2 greater than 0.80 AND PEEP greater than 14 cm H₂O
2. Hemodynamic instability (despite fluid resuscitation/pressor support)
3. Open external ventricular device or intracranial pressure greater than 15mmHg or unstable
4. INR greater than 2.0 (within 36 hours of BAL)
5. Platelets less than $50 \times 10^3/\text{mm}^3$ (within 36 hours of BAL)

Since this is a study procedure, any associated adverse event should be reported as a study-related event. Transient hypoxemia is considered an expected event for ALI, but prolonged or severe hypoxemia following mini-BAL should be reported as an adverse event.

I. Conservative Fluid Management Algorithm

This fluid protocol captures the primary positive outcome of the FACTT trial on increasing ventilator free days. This protocol should be initiated within four hours of randomization in enrolled patients and continued until UAB or study day seven, whichever occurs first.

1. Discontinue maintenance fluids.
2. Continue medications and nutrition.
3. Manage electrolytes and blood products per usual practice.
4. For shock, use any combination of fluid boluses[#] and vasopressor(s) to achieve MAP = 60 mmHg as fast as possible. Wean vasopressors as quickly as tolerated beginning four hours after blood pressure has stabilized.
5. Withhold diuretic therapy in renal failure^{**} and until 12 hours after last fluid bolus or vasopressor given.

CVP (recommended)	PAOP (optional)	MAP \geq 60 mm Hg AND off vasopressors for \geq 12 hours	
		Average urine output < 0.5 ml/kg/hr (PBW)	Average urine output \geq 0.5 ml/kg/hr (PBW)
> 8	> 12	Furosemide* Reassess in 1 hour	Furosemide* Reassess in 4 hours
4-8	8-12	Give fluid bolus as fast as possible [#] Reassess in 1 hour	No intervention Reassess in 4 hours
< 4	< 8	Reassess in 1 hour	No intervention Reassess in 4 hours

[#] Recommended fluid bolus= 15 mL / kg (PBW) crystalloid (round to nearest 250 mL) or 1 Unit packed red cells or 25 grams albumin

* Recommended Furosemide dosing = begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg / day. Also, if patient has heart failure, consider treatment with dobutamine.

**Renal failure: dialysis dependence, OR oliguria with serum creatinine greater than 3 mEq/dl, OR serum oliguria with creatinine 0-3 mEq/dl with urinary indices indicative of acute renal failure.

J: LONG TERM OUTCOMES

Phone Surveys for Survivors from All 12 ARDSNet Study Sites

Table 1 summarizes the proposed measurement instruments and their rationale for each of the outcome domains evaluated in the phone-based assessments of ALI survivors from all ARDSNet study sites. These domains and instruments were determined based on a comprehensive assessment performed by the ARDSNet Long-Term Outcomes Committee and by the investigators for this proposed study.

Table 1. Phone assessments of ALI survivors from all 12 ARDSNet study sites at 6 and 12 months

Outcome Domain	Instrument	Rationale	No. of items; Time Req'd; Scale
Mortality	Custom (date & cause of death)*	- Used in existing long-term ALI study(6)	3 item; <1 min.
Physical function	Functional Performance Inventory - Short Form (FPI-SF)	-Developed in chronic pulmonary patients -Comprehensive, reliable and valid(129;130)	32 items; 5 minutes; Continuous
Mental health			
a) Depression & General Anxiety	Hospital anxiety & depression (HAD) scale(131)	-Most widely used survey in medical patients(132) -Separate subscale for depression & anxiety -Reliable and validated in medical patients(132) -Highly correlated with psychiatric evaluation(131;133)	14 items; 5 minutes(6) Continuous
b) Post-traumatic stress disorder	Impact of Events Scale – Revised (IES-R)(134)	-IES is the most commonly used instrument for assessing PTSD in the ICU(133) -Revised version (IES-R) follows DSM-IV(135) criteria -Reliable and valid(134;136)	22 items; 3 minutes(6) Continuous
Cognitive status	Telephone Mini-Mental State Examination (TMMSE)(137;138)	-MMSE is the most widely used instrument -TMMSE is designed specifically for phone use -Reliable and valid(137;138)	16 items; 5 minutes; Continuous
Health-related quality of life			
a) Generic	1. SF-36 version 2 (139)	-Most widely used instrument, esp in ALI(4;6;7;17;18) -Reliable and validated in ICU patients(141) -US population norms available(139)	36 items; 6 minutes; Continuous
	2. EQ-5D (EuroQOL) (140)	-Feasible for patients with inattention& fatigue(17;140) -Recommended for use in ICU patients(14) -Provides utility estimate with US norms(142)	6 items; 2 minutes(6) Continuous
b) Fatigue	Functional Assessment of Chronic Illness Therapy (FACIT)	-Designed for patients with chronic illness -Assesses both functional & emotional impact(143;144) -Reliable and validated(145;146)	13 items; 3 minutes(143) Continuous
Return to work	Custom instrument	-Developed & used in large cohort of ALI survivors(6)	12 item; 2 min. Categorical
Health care utilization	University of Toronto ARDS Outcome study instrument(12)	-Developed and used in large longitudinal cohort of ALI survivors(12)	27 items; 8 minutes; Continuous

* Also will be determined from National Death Index via participant's Social Security Number.

Administration of phone surveys will be centralized at 2 sites: Johns Hopkins and LDS Hospital, where the 2 Principal Investigators are affiliated. Being in different time zones, this 2-site approach will allow flexibility in accessing patients across the US while also concentrating our oversight activities. Manuals of Operations will be used for training, reference and quality assurance review.

NOTES:

(1) Estimated time for completion. This was based on pilot testing, published estimates and the experience of the ARDS Network investigators. The full telephone interview will be piloted prior to implementation (2) Return to Work assessment. There are no pre-existing comprehensive survey instruments for measuring return to work and work disability in patients with lung disease. We derived our custom-made instrument from an approach used by one member of the Long-term Outcomes Committee (Dr. Eisner and colleagues) to measure work disability in asthma and COPD.

J.2 Statistical Considerations for Long Term Outcomes

A number of dichotomous and continuous measures of long-term efficacy of the treatment will be analyzed.

Dichotomous measures:

- 1) Survival times will be compared for the treatment arms using log rank test.
- 2) Proportions of patients alive without major disabilities will be compared between the treatment arms using Cochran-Mantel-Haenszel test. Major disability is defined for surviving patients that are prevented from working due to a respiratory condition.
- 3) Proportions of patients alive without disability in activities of daily living (ADL) or instrumental activities of daily living (IADL) will be compared across treatment arms using Cochran-Mantel-Haenszel test. Major disability ADL and IADL are defined based on functional performance inventory for a patient who has at least one activity in the “body care” and “maintaining household” subscales, respectively, that s/he cannot perform at all due to health reasons or does it with much difficulty.

Each of the comparisons will be done based on the data collected at 6 months, and 1-year follow up times.

Continuous measures:

- 1) Primary measure of disability defined by functional performance inventory.
- 2) Eight subscales and two summary measures of the SF-36 instrument
- 3) Depression measure defined by Beck Depression Inventory II
- 4) Cognitive measure

Continuous measures will be analyzed using analysis of variance stratified by the treatment arm.

Each of the comparisons we will be done based on the data collected at 6 months, and at 12 months follow up times. We will compare the raw continuous measures in the groups of patients available for the follow up. There is a concern that those patients that survive and are contactable to obtain information will potentially belong to different populations for different treatment arms. If true, this will make comparison between the treatment

arms no longer randomized. To address this we will compare the treatment arms using survival average causal effect (SACE). This method (Hayden 2005) uses concepts of casual inference by adjusting the estimates of the population parameters based on the model covariates. First the expected probabilities of survival and ability to contact and obtain information from a patient are computed using logistic regression. Then estimates are weighted by these computed survival and contactability to correct for potential differences in the patient populations across treatment arms selected by survival and contactability of patients. The model depends on the assumption that conditional on the values of the covariates the probabilities of a patient surviving and being contactable are independent across treatment arms. The effects of this assumption will be evaluated via a sensitivity analysis.

J.3 Citations for J1 (Choice of survey instruments)

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K Dead-Space Measurement

Procedure for the ARDS Network Studies at Selected Sites

Measurement of pulmonary dead space makes it possible to assess physiologically a defect in gas exchange that cannot be done with any other method. Based on work from Dr. Matthay's research group (*NEJM* 2002) and additional work from Dr. Gattinoni's research group (*NEJM* 2006), abnormalities in dead space fraction have pathogenetic and prognostic significance. It is possible that one or more the treatments to be tested in the ARDS net ALTA or Nutrition trials will favorably impact the pulmonary dead space fraction, thus contributing to more rapid extubation and more ventilator free days. We cannot make the measurement at all sites but will have at least 30-40% of the participating hospitals make this noninvasive measurement at baseline and on subsequent days. This information will also enrich the overall pathophysiologic understanding of acute lung injury.

Equipment Needed:

1. NICO model 7300 pulmonary monitor (Respironics, Inc)
2. Novamatrix capnostat probe model # 9567-00
3. NICO CO₂/Flow sensor # 9767 (adult) for endotracheal tube sizes ≥ 5.5 mm ID. This sensor has a measurement range of 2-180 L/min for flow rates, 0.20 to 3.0 L for tidal volume and a mechanical dead-space of < 8.5 mL.
4. Alternatively, a NICO CO₂/Flow sensor #9766 (pediatric) for endotracheal tube sizes 3.5-6.0 mm ID. This sensor has a measurement range of 0.5-100 L/min for flow rate, 30 to 400 mL for tidal volume and a mechanical dead-space of < 4 mL.

5. Arterial blood gas procurement kit.

Procedure:

Patient Preparation:

Neither nursing care nor respiratory care activities should occur in the peri-measurement period that would likely change either the breathing pattern, hemodynamic state or metabolic rate. Suctioning and aerosol drug administration should occur approximately 20-30 minutes prior to the dead-space measurements. Whenever possible, patients should be positioned in a low-Fowlers position, with either no or minimal rotation.

Patients enrolled in the ARDS network trials are to be managed with the NIH ARDS Network low V_T ventilation protocol. Therefore, the ventilator should be in the volume assist-control mode to guarantee as consistent delivery of V_T (approximately 6 mL/kg predicted body weight) and minute ventilation as possible. Dead-space measurement should not be done on patients who are not on assist control mode.

In the presence of patient-ventilator asynchrony and/or agitation, the following steps should be taken in the following order:

- a) Adjust the peak inspiratory flow rate is ≥ 75 L/min and trigger sensitivity to -1 cm H₂O (or flow trigger ~ 1-2 L/min).
- b) When these changes cannot adequately control the ventilatory pattern, then the V_T should be adjusted upwards by 1 mL/kg to a maximum of 8 mL/kg for the procedure.

Infection Control

Follow all local infection control procedures when executing dead-space measurements. The following general infection control procedures should be followed:

- a) Thorough hand-washing and clean gloves should be worn when the Capnostat and flow sensor is placed and removed from the ventilator circuit.
- b) When the same practitioner is handling both the ventilator circuit and obtaining blood from the arterial line, thorough hand-washing and glove changes must occur prior to obtaining blood. This is to prevent the possibility of arterial line contamination from handling the ventilator circuit.
- c) Because the NICO monitor will be used on multiple patients, it is imperative that a disinfectant approved by the hospital be used to thoroughly clean both the monitor and the Capnostat cable after it has been removed from a patient's room and prior to the next measurement.

Because the flow sensor can be reused, it should be placed in a clean specimen bag and kept in the patient's room.

Set-Up

1. Connect NICO unit to wall power source.
2. Insert Capnostat probe into the front of the NICO unit until a "click" is heard.
3. When using a new CO₂/Flow sensor, check the sensor for any damage. If damage is noted, replace the sensor.
4. Attach the CO₂/Flow sensor to the Capnostat probe. The sensor is properly seated on the probe when a "click" is heard.
5. Power-on the NICO monitor.

6. Press the MENU button on the front of the monitor.

NOTE: To maneuver between functions and menus on the NICO rotate the thumb wheel on the front of the unit to highlight a function on the screen and then select that function by depressing the thumb wheel

7. Select the SET-UP function.
8. Select CO₂ ZERO NOW (It may take a few minutes for the sensor to warm-up before the test can be executed).

Dead-Space Measurement

1. Place the Capnostat probe in the ventilator circuit at the Y-Adapter.
2. Press the MENU button on the front of the monitor again.
3. Select TABULAR DATA
4. Allow the NICO to collect data for approximately 10 minutes to monitor the stability of the mean PeCO₂ and CO₂ minute production (\dot{V}_{CO_2}). In a quasi-“steady state”, PeCO₂ and \dot{V}_{CO_2} should not vary by more than 1 mm Hg and ~10 mL/min within a 5 minute period.
5. During this initial monitoring period, perform a ventilator status check and record the information onto the dead-space/ventilator parameters case report form. Insure that a 0.5 sec end-inspiratory pause time is used to measure the plateau pressure. When possible, perform an end-expiratory pause maneuver to measure the presence of any intrinsic PEEP.
6. Once PeCO₂ and \dot{V}_{CO_2} measurements are reasonably stable, use aseptic technique to obtain an arterial blood gas.
7. Withdraw enough arterial line flush fluid until a thick layer of blood coats the bottom of the “waste syringe”.
8. Note the time on the NICO tabular screen when beginning the actual sample aspiration. Aspirate blood into the heparinized syringe slowly over approximately a 1-minute period so that the blood gas sampling time approximates the expired gas sampling time.
9. Remove any large air bubbles in the blood gas sample then cap the sample and place on ice

NOTE: Avoid using an ice water “bath” as plastic syringes may allow fluid absorption that can affect the PaCO₂ results).

10. Deliver the arterial blood gas to the laboratory.
11. Once the blood gas results have been obtained then do the following:
12. On the TABULAR screen, highlight the TIME and depress the thumb wheel to confirm the entry. Rotate the thumb wheel to move the screen back in time to select the minute used for the arterial blood gas sampling.
13. Record the following information on the case report form: PeCO₂, \dot{V}_{CO_2} , the expired mechanical tidal volume (V_T e-m), Airway dead space (V_d AW) and the end-tidal PCO₂.

NOTE: When using the Tabular Data screen each column can be formatted so that the required variables are always displayed. To change the displayed variable in any column, rotate the thumb wheel to move the highlight to the desired column and depress the thumb wheel to confirm the entry. Then rotate the thumb wheel again to change the displayed variable and depress the thumb wheel to confirm the entry.

14. Press the DATA ENTRY button on the front of the monitor.
15. Select the INSPIRED O₂ %, and then rotate the thumb wheel to adjust the digital read-out so that the % oxygen concentration is the same as the FiO₂ used during the test. Depress the thumb wheel to confirm the entry.
16. Return to the DATA ENTRY screen and select ABG ENTRY. Use the thumb wheel to select and enter the PaO₂ and PaCO₂ results from the arterial blood gas. In addition, the most recent available hemoglobin or hematocrit value must be entered.
17. SELECT the ABG TIME and enter the time when the blood gas was drawn and depress the thumb wheel to confirm the entry. The NICO monitor will calculate and display both the dead-space fraction and the alveolar dead-space in mL in addition to the time the measurement was made. Enter these variables onto the paper case report form.

NOTE: The most recent dead-space fraction and alveolar dead-space are displayed on the SINGLE BREATH CO₂ screen. Beware that the displayed PeCO₂ on this screen is a real-time measurement that may be different from the value obtained when the ABG was obtained. Therefore, all other variables must be obtained from the TABULAR DATA screen.

18. After data recording has been completed remove the Capnostat and flow sensor and follow the infection control procedures listed above.
19. Enter data from the paper case report form into the Accelere database and keep all paper records in a secured shadow chart for each patient.

L AUDIT Questionnaire

The Alcohol Use Disorders Identification Test (Babor 1992)

The Alcohol Consumption Questionnaire is important to administer because there is a common association between alcohol abuse and Acute Lung Injury (ALI) (Moss 1996). It will be important to have this information for a subgroup analysis. Knowledge of alcohol abuse will also help the primary team better care for the patient and improve patient outcome, as there are alcohol specific disorders in critically ill patients that often are not diagnosed and therefore not treated effectively. This survey should be completed by the surrogate or subject (but not for subjects less than 18 years of age).

<p>1. How often do you have a drink containing alcohol?</p> <p>(0) Never (Skip to Qs 9-10) (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week</p> <input type="checkbox"/>	<p>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <input type="checkbox"/>
<p>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</p> <p>(0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more</p> <input type="checkbox"/>	<p>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <input type="checkbox"/>
<p>3. How often do you have six or more drinks on one occasion?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <p><i>Skip to Questions 9 and 10 if Total Score for Questions 1 and 3 is 0.</i></p> <input type="checkbox"/>	<p>8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <input type="checkbox"/>
<p>4. How often during the last year have you regretted that you were not able to stop drinking once you had started?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <input type="checkbox"/>	<p>9. Have you or someone else been injured as a result of your drinking?</p> <p>(0) No (2) Yes, but not in the last year (4) Yes, during the last year</p> <input type="checkbox"/>
<p>5. How often during the last year have you failed to do what was normally expected from you because of drinking?</p> <p>(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily</p> <input type="checkbox"/>	<p>10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?</p> <p>(0) No (2) Yes, but not in the last year (4) Yes, during the last year</p> <input type="checkbox"/>
<p>Record total of specific items here: <input type="checkbox"/></p> <p><i>If total is greater than recommended cut-off, consult User's Manual.</i></p>	

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**Amendment 5 to ARDSNet Study 06
ALTA Protocol Version II
Amendment issue date: April 29, 2008**

Amendment 5

Section 4.3, number 9

Insert the bolded language as **9d**.

9. Administration of the following:

d. Methylprednisolone equivalents greater than 20 mg