

Randomized Trial of Rosuvastatin for Acutely Injured Lungs from Sepsis

SAILS: Statins for Acutely Injured Lungs from Sepsis

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ABBREVIATIONS

ABG = Arterial blood gas
AKI = Acute Kidney Injury
ALI = Acute Lung Injury
ALT = Alanine transaminase
APACHE=Acute physiologic and chronic health evaluation
ARDS = Acute Respiratory Distress Syndrome
AST = Aspartate aminotransferase
AUC= Area under the curve
AUDIT= Alcohol Use Disorders Identification Test
BIPAP= Bi-level Positive Airway Pressure
BMI = Body Mass Index
CCC = Clinical Coordinating Center
CK = Creatinine Kinase
CLP=Cecal ligation and puncture
CTPA/V = Computerized Thoracic Pulmonary Angiography and/or Venography
CPAP = Continuous Positive Airway Pressure
CRP = C-reactive protein
Day 0 = Day of Randomizations
DSMB = Data Safety Monitoring Board
EPAP = Expiratory Positive Airway Pressure
FACTT = Fluid and Catheter Treatment Trial
FDA=Food and drug administration
FiO₂ = Fraction of Inspired Oxygen
GCS = Glasgow Coma Scale
HR = Hazard Ratio
ICU = Intensive care Unit
IFN- α = Interferon-gamma
IL-6 = Interleukin 6
IMV = Intermittent Mechanical Ventilation
IRB = Institutional Review Board
IVRS = Interactive Voice Response System

LPS = lipopolysaccharide
MBW = measured body weight
MCP-1 = Monocyte chemotactic protein-1
NF- κ B= Nuclear factor kappa B
NHLBI = National Heart Lung and Blood Institute
NIV= Non-invasive ventilation
NOS= Nitric oxide synthase
OR = Odds Ratio
OI = Oxygenation Index defined as mean airway pressure x F₁O₂/PaO₂
PaCO₂ = Partial pressure of arterial carbon dioxide
PaO₂ = Partial pressure of arterial oxygen
PB = Barometric Pressure
PBW = Predicted Body Weight
PCV = Pressure Control Ventilation
PEEP = Positive End-Expiratory Pressure
PEG = Percutaneous Endoscopic Gastrostomy
PIN = Personal Identification Number
Pplat = Plateau pressure
PS = Pressure Support Ventilation
PAOP = Pulmonary Artery Occlusion Pressure
RAGE = receptor for advanced glycation end products
RCT = Randomized Controlled Trial
SBT = Spontaneous Breathing Trial
SIRS = Systemic Inflammatory Response Syndrome
SOFA=Sequential organ failure assessment
SpO₂ = Oxygen Saturation
VFD = Ventilator-free Day
VTE= Venous thromboembolism
ULI = Unilateral Lung Injury
ULN = Upper limits of normal
VTE=Venous thromboembolism; includes deep venous thrombosis and pulmonary thromboembolism
vWF = von Willebrand factor

DEFINITIONS

Acute Kidney Injury: Acute kidney injury network Stage 3 disease, defined as a threefold increase in creatinine from baseline or the need for dialysis

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

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.

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.

Extubation: Removal of an orotracheal, nasotracheal tube, or unassisted breathing with a tracheostomy

Home: level of residence or health care facility where the patient was residing prior to hospital admission

Hospital Mortality to Day 60: This primary endpoint includes all deaths following randomization in any health care facility prior to discharge “home” until study day 60. Study subjects still in a health care facility at study day 61 are considered alive for this endpoint.

NYHA: 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 an anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased).

Sepsis: SIRS criteria plus suspected or known infection. Since intubation and hypoxemia is a requirement for enrollment into this trial, participants will, by definition, meet the respiratory SIRS criterion. They must also meet two of three non-respiratory SIRS criteria.

Study hospital: Defined as the hospital where the patient was randomized and enrolled.

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.

UAB (Unassisted Breathing): Spontaneously breathing with face mask, nasal prong oxygen, or room air, T-tube breathing, tracheostomy mask breathing, or CPAP ≤ 5 without PS or IMV assistance, or the use of noninvasive ventilation solely for sleep-disordered breathing. Assisted breathing is any level of ventilatory support at pressures higher than the unassisted breathing thresholds.

Part I: Study Summary

Title: Randomized Evaluation of Rosuvastatin for Acutely Injured Lungs from Sepsis

Objective: To assess the efficacy and safety of oral rosuvastatin in patients with sepsis-induced Acute Lung Injury (ALI).

Hypothesis: Rosuvastatin therapy will improve mortality in patients with sepsis-induced ALI.

Study Design:

1. Multi-center, prospective, randomized, placebo-controlled clinical trial
2. A maximum of 1000 patients will be enrolled
3. Participants will be randomized to receive either rosuvastatin or placebo
4. Treatment will continue for 28 days, discharge from study hospital or death, whichever comes first.
5. All participants will be followed for 7 days following the last dose of study drug for adverse events. Participants will also be followed to the earlier of discharge home on UAB or day 60.

Sample Size/Interim Monitoring:

1. The principal analysis will be on the basis of the intention-to-treat.
2. The primary outcome is hospital mortality to day 60. With a sample size of a 1000 patients, the study has a 92% probability of detecting a mortality benefit if the true difference in mortality is 9% (from 27% to 18%) with rosuvastatin.
3. Trial progress will be monitored by an independent Data and Safety Monitoring Board to determine if the study should stop for safety, futility, or efficacy. The first analysis will occur after the enrollment of 100 patients and will include a review of rosuvastatin plasma levels on the first 30 rosuvastatin-treated patients will be reviewed. The next review will be after enrollment of 250, and further reviews will occur after enrollment of 500 and 750 patients. The DSMB will also monitor trial quality and feasibility.

Inclusion Criteria: Patients with ALI from sepsis will be enrolled as defined below. Patients with ALI caused by sepsis are being targeted as the majority of supporting animal and human studies focus on the effect of statins on infection induced inflammation as opposed to trauma and transfusion related inflammation and lung injury.

1. Systemic inflammatory response syndrome (SIRS), defined as meeting at least 1 of the following 3 criteria for a systemic inflammatory response. One of the SIRS criteria must be either the WBC criteria (a) or the body temperature criteria (b) :
 - a. White blood cell count $>12,000$ or $<4,000$ or $>10\%$ band forms
 - b. Body temperature $>38^{\circ}\text{C}$ (any route) or $<36^{\circ}\text{C}$ (by core temperatures only: indwelling catheter, esophageal, rectal)
 - c. Heart rate (> 90 beats/min) or receiving medications that slow heart rate or paced rhythm
2. Suspected or proven infection: Sites of infection include thorax, urinary tract, abdomen, skin, sinuses, central venous catheters, and central nervous system (Appendix A).

3. ALI as defined by acute onset of:
 - a. $\text{PaO}_2 / \text{FiO}_2 \leq 300$ (intubated). If altitude $> 1000\text{m}$, then $\text{PaO}_2 / \text{FiO}_2 \leq 300 \times (\text{PB}/760)$, and
 - b. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph, and
 - c. Requirement for positive pressure ventilation via an endotracheal tube, and
 - d. No clinical evidence of left atrial hypertension, or if measured, a Pulmonary Arterial Wedge Pressure (PAOP) less than or equal to 18 mm Hg. If a patient has a PAOP > 18 mmHg, then the other 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 patchy or diffuse opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (>28 days). The findings of vascular redistribution, indistinct vessels, and indistinct cardiac borders are not considered “consistent with pulmonary edema”.

All ALI criteria (3a-d above) must occur within the same 24 hour period. The onset of ALI is when the last ALI criterion is met. Patients must be enrolled within 48 hours of ALI onset and no more than 7 days from the initiation of mechanical ventilation. SIRS criteria must occur within the 72 hours before ALI onset **and the 24 hours after ALI onset**. Information for determining when these time window criteria were met may come from either the Network hospital or a referring hospital reports.

Exclusion Criteria:

1. No consent/inability to obtain consent
2. Age less than 18 years
3. More than 7 days since initiation of mechanical ventilation (**Example: If day of randomization is day “zero”, date of current intubation cannot be prior to day “negative 7”**)
4. More than 48 hours since meeting ALI inclusion criteria
5. 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)
6. Unable to receive or unlikely to absorb enteral study drug (e.g. patients with partial or complete mechanical bowel obstruction, intestinal ischemia, infarction, and short bowel syndrome)
7. Rosuvastatin specific exclusions
 - a. Receiving a statin medication within 48 hours of randomization
 - b. Allergy or intolerance to statins
 - c. Physician insistence on the use of or avoidance of statins during the ICU stay

- d. CK, ALT or AST > 5 times the upper limit of normal (ULN) except in patients with elevated CK who have an identifiable cause of CK elevation other than statin therapy providing the CK levels have fallen at least 10 % in the two most recent measurements **and** are less than 10 times ULN at randomization and the patient had not received any statins in the 30 days prior to enrollment (**Example:** A patient with staphylococcal sepsis has a CK of 3000 (10 times ULN). The next measurement is 2400 (8 times ULN). This patient would not be excluded for the elevated CK provided that no statins had been administered in the previous 30 days because the CK is now less than 10 times ULN, and the value has fallen more than 10% in the last two measurements).
 - i) If not available, a blood sample will be obtained after informed consent and results must be below protocol specified thresholds prior to randomization..
 - ii) CK, ALT and AST values obtained up to 24 hours prior to randomization are acceptable baseline values (e.g. Day zero) for both randomization and administration of the first dose of study.
- e. Diagnosis of hypothyroidism and not on thyroid replacement therapy
- f. Pregnancy or breast feeding
- g. Receiving niacin, fenofibrate, cyclosporine, gemfibrozil, lopinavir, ritonavir, atazanavir, daptomycin while on study drug
- 8. Severe chronic liver disease (Child-Pugh Score 12-15)
- 9. Moribund patient not expected to survive 24 hours
- 10. Chronic respiratory failure defined as PaCO₂ > 60 mm Hg in the outpatient setting
- 11. Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing
- 12. Diffuse alveolar hemorrhage from vasculitis
- 13. Burns > 40% total body surface area
- 14. Interstitial lung disease of severity sufficient to require continuous home oxygen therapy
- 15. Unwillingness or inability to utilize the ARDS network 6 ml / kg PBW ventilation protocol
- 16. Cardiac disease classified as NYHA class IV
- 17. Myocardial infarction within past 6 months
- 18. Intraparenchymal Central Nervous System (CNS) bleed within a month of randomization.

Efficacy: The primary efficacy variable is Hospital Mortality to day 60.

Secondary Efficacy Variables:

- 1. Ventilator Free Days to day 28
- 2. Hospital mortality to day 28
- 3. Organ failure free days at day 14
- 4. ICU-free days at day 28
- 5. Hospital-free days at day 60

6. Increase in PaO₂/FiO₂ ratio and reduction in Oxygenation Index on study days 1-7 (to use ABGs as available)
7. Venous thromboembolism (VTE) to day 14
 - a. Documented by venous ultrasound, impedance plethysmography, contrast venography, ventilation-perfusion lung scan, CTPA/V, or pulmonary angiography
8. Composite end-point of myocardial infarction, bowel ischemia or ischemic stroke to study day 28
9. Arrhythmias during ICU stay or until day 14, whichever is first
10. Development of acute kidney injury (AKI)
11. Changes in plasma concentrations of CRP from day 0 to day 6 and day 14. Blood and urine will be reserved beyond study completion for additional biomarker studies.

Focused Safety Analysis: Incidence of elevations in CK > 10 times ULN or ALT > 8 times ULN as measured on days 0,1,3,6,14,21 (Appendix B)

Study Drug Dosing: All study drug doses will be administered via the enteric or oral route. Study drug will be blinded using an identical appearing placebo.

1. The first study drug dose (rosuvastatin or placebo) will be administered within 4 hours of randomization as a loading dose of 40 mg.
2. Subsequent doses will be at 10 am daily (+/- 4 hours) starting on the next calendar day as a maintenance dose of 20 mg.
 - a. If for any reason a maintenance dose is not administered at the intended time, it may be administered subsequently but not more than 12 hours after the intended time of administration.

Should the time be > 12 hours since last scheduled dose, the patient will not receive a dose on that study day but will be given a loading dose on the next calendar day. Maintenance dosing will continue on subsequent days.

Daily doses will be reduced by 50% for patients with a creatinine level of greater than or equal to 2.8 mg/dL who are not on renal replacement therapy. Loading doses will not be reduced.

Daily Dosing:

- Each subject will receive full dose if last known creatinine value is less than 2.8 mg/dL.
- Each subject will receive half dose if last known creatinine value is greater than or equal to 2.8 mg/dL (unless receiving renal replacement therapy in which case a full dose is given).

If used, antacids should be administered no closer than 6 hours before or after administering rosuvastatin to avoid affecting absorption of study drug.¹ The dosage need not be adjusted for concomitant use of ketoconazole, erythromycin, itraconazole, fluconazole, warfarin or digoxin.

Drug level specimens (venous blood): The 40 mg loading dose and 20 mg maintenance dose are midrange doses and were selected based on the desire to quickly achieve and maintain plasma levels of rosuvastatin in the range of 10-70 ng/ml (see pharmacokinetic information

below). However, to verify adequate absorption of rosuvastatin, blood for peak and trough plasma rosuvastatin levels will be obtained on day 6 (+/- 2 days) in the first 60 patients and analyzed in the approximately 30 patients randomized to rosuvastatin. Trough levels will be drawn prior to the day 6 (+/- 2 day) dose. Peak levels will be drawn 3-5 hours after the dose.

The target plasma range for modifying lipid metabolism, as measured 3-5 hours after the day 6 (+/- 2 days) dose is expected to be between 10-70 ng/ml of rosuvastatin based on pharmacokinetic studies and reported half life of 10-20 hours.²⁻⁷ If mean plasma levels are lower than 10 ng/ml then the Steering Committee will consider increasing rosuvastatin loading and/or maintenance doses. If mean plasma levels are greater than 70 ng/ml, then the decision to modify the current dose will be based primarily on safety and early indications of efficacy. A formal recommendation regarding dose adjustments for high drug levels is not possible as the relationship, if any, of plasma levels to either the pleiotropic effects or the toxicities of statins is unknown. Dose changes will be recommended by the investigators and independently reviewed by the DSMB who will have unblinded access to the drug levels, adverse events, clinical and laboratory findings, and study outcomes.

Completion of study drug administration: Study drug administration will be stopped when one of the following conditions is met, whichever comes first:

1. 28 days after randomization or three days after ICU discharge (whichever occurs first)
2. Discharge from study hospital
3. Death

Note: If patient is readmitted to the ICU while still on study drug for three days after subsequent ICU discharge or day 28, whichever occurs first. If a patient is readmitted to the ICU after study drug has already been stopped per protocol, it does NOT get restarted when readmitted to the ICU.

Part II: Study Description

Randomized Trial of Rosuvastatin for Acutely Injured Lungs from Sepsis

SAILS: Statins for Acutely Injured Lungs from Sepsis

1. Background

1.1. Introduction

Pneumonia and extrapulmonary sepsis account for 50-65% of all ALI cases and mortality is high.⁸⁻¹¹ Over the past decade, several observational studies have reported that patients admitted for treatment of infection and/or sepsis and who were taking a statin as an outpatient have significantly lower mortality and morbidity than patients not receiving a statin. These findings are especially notable because the patients who had received statins had more comorbid conditions such as hypertension, diabetes, coronary artery disease, COPD, renal dysfunction and stroke.¹²⁻¹⁹

1.2. Observational Trials of Statins in Sepsis and ALI /ARDS

Almog et al. prospectively examined the outcomes of patients with sepsis who had received statins for at least one month prior to admission.¹⁷ Despite the statin therapy group having a higher baseline incidence of hypertension, ischemic heart disease, diabetes, and a trend toward more congestive heart failure, patients on statins were less likely to progress to severe sepsis and end-organ dysfunction. The risk of developing severe sepsis was lower by 16.6% (19 to 2.4%, $p=0.001$) (relative risk reduction of 87%). Furthermore, the relative risk of death was 0.43 (8.6 to 3.7%, $p=0.14$). Sixty percent of those developing severe sepsis had 2 or 3 organ failures and one third developed 4-organ failure. Of the 55 patients who developed severe sepsis, only 2 were in the statin group (personal communication, Y. Almog). Unlike most reported observational studies with statins in this population, statin therapy was continued after admission in 75% of patients (personal communication Y. Almog). The Irish Critical Care Trials Group reported that patients on statins with ALI had a trend toward reduced mortality (33.5% to 20.8%).²⁰ Both publications did not report any toxicity attributable to statins.

In a retrospective study of 388 hospitalized patients with bacteremia, 35 had been taking statins and 353 had not. Mortality was lower in those taking statins (6% vs. 28%, $p=0.002$).¹⁴ Attributable mortality from bacteremic sepsis was 20% in patients who had not been taking statins and 3% for those who had been taking statins ($p=0.01$). The reduction in mortality remained significant after multivariate analysis with an odds ratio of 7.6 (CI: 1.01–57.5). Patients on statins were more likely to have diabetes, hypertension, and coronary artery disease.

No patients in the statin group developed a nosocomial bacteremia vs. 27% in the group not receiving statins.¹⁴ No toxicity related to statin use was reported.

Kruger et al. recently published a retrospective analysis of patients admitted with sepsis¹³. Sixty-six of 438 patients were on statin therapy at the time of hospital admission. The patients on outpatient statin therapy were more likely to have diabetes, hypertension, and congestive heart failure and were less likely to be immunosuppressed. All cause mortality was higher in the non-statin group (23.1% vs.10.6%; $p = 0.022$). Mortality specifically attributable to bacteremia was lower in statin users (6.1% v 18.3%, $p=0.014$). Fifty-six of 66 patients in the statin group were continued on statin therapy during the hospitalization and had an all cause mortality of 1.8% as opposed to 23.1% for never-statin users ($p=0.0002$). Mortality attributable to bacteremia was also reduced (1.8% vs. 18.3%; $p=0.0018$) and no toxicity from statins was reported.

Hackam et al. evaluated the incidence of sepsis in patients over 65 years of age surviving at least 3 months after hospitalization for an acute coronary syndrome, ischemic stroke or revascularization.²¹ Of 141,487 patients, 46,662 were discharged on statin therapy. Using propensity matching, two comparable cohorts were identified (34,584 patients on statin therapy and 34,584 not on statin therapy). The incidence of sepsis during follow up was 71.2 vs. 88.0 per 10,000 patient-years (hazard ratio of 0.81; 95% CI 0.72-0.91).

Thomsen et al. retrospectively evaluated outcomes in nearly 30,000 Danish patients hospitalized for pneumonia, of which 4.6% were taking statins prior to admission.¹⁶ The mortality rate ratios were significantly lower in statin users at 30days and 90days (0.69 and 0.75 respectively). In a prospective observational study by Chalmers et al. of 1007 patients admitted with community acquired pneumonia, statin users had a reduced 30 day mortality (adjusted OR 0.46, 95%CI 0.25-0.85, $p=0.01$) and reduced incidence of complicated pneumonia (adjusted OR 0.44, 95%CI 0.25-0.79, $p=0.006$).²² However, there was no reduction in application of mechanical ventilation or inotropic support. The statin group had reduced CRP values on admission (medians 119 vs. 182, $p<0.0001$).

Donnino et al. reviewed outcomes in patients admitted through the emergency department (ED) for suspected infection.¹² Twenty three percent of 2036 patients had a statin administered after ED admission. Despite greater comorbidities in the patients receiving statins, mortality was lower by 73%. The investigators have begun an RCT to evaluate statins for patients admitted with suspected sepsis. Schmidt reported reduced mortality in patients with multiple organ dysfunction between statin users versus non-statin users (28 day mortality 33% vs. 53%, $p=0.03$ and hospital mortality 72% vs. 35% $p<0.0001$).¹⁵ Donnino and Schmidt did not report any toxicity attributable to statins.

Taken together, these published observational studies show an association between statins and improved outcome in patients with sepsis and bacteremia with no reported toxicity. However, it is not clear if this association is causal or explained by other factors such as better access to healthcare for patients receiving statins. This is in part addressed by a study of Shah et al. examining a cohort from Kaiser-Permanente health care system where all patients have access to health care within the Kaiser system.¹⁸ Patients admitted with a diagnosis of sepsis, SIRS, septic

shock or ARDS were separated into three groups; current statin users, remote users (history of statin usage but not within 2 months before admission) and nonusers (no statin usage in the 12 months preceding hospitalization). Over 23,000 patients aged > 50 years were identified. After adjusting for age and gender only, the mortality hazard ratios were lower in current users than non users (0.78) and, after adjustment for differences in co-morbidities and Charlson scores, current users had lower mortality hazard ratios than remote users and non users (0.80 and 0.85 respectively). Statin users had significantly reduced mortality hazard ratios in comparison to remote and nonusers. Shah et al. have also shown that the mortality benefit observed in the statin users was greater in those on higher statin doses, suggesting a dose response.¹⁹

1.3. Randomized Trials of Statins for Sepsis

Two prospective RCTs involving the acute use of statins in patients with sepsis who were not on statins prior to hospitalization have been presented but have not yet been published except in abstract form. These two trials are summarized below.

Choi et al. studied atorvastatin (10 mg daily) in 67 patients with sepsis and pneumonia.²³ Baseline APACHE III score, acute lung injury score, pneumonia severity index, and SOFA score at admission, ICU stay and hospital stay were not different between groups. Day 1 cholesterol values were not different between two groups, but Day 7 cholesterol was lower in statin group (92 mg/dl vs. 115 mg/dl, p=0.044). Hospital mortality was reduced in the atorvastatin group as compared to placebo (27.3% vs. 55.9; p=0.026). No adverse events were attributed to atorvastatin.

Montoya et al. conducted an RCT of 80 mg/day simvastatin or placebo for 14 days in 40 patients with sepsis. Simvastatin decreased CRP and an increased Anti-thrombin III. While a shorter length of stay was seen, no differences in survival were noted.²⁴

1.4. Negative Observational Trials and Clinical Equipoise

Published observational studies are not unanimous in demonstrating an association between statins and better outcomes, thus supporting equipoise for a randomized controlled trial. Yang et al. found no benefit of prior statin therapy in an Asian population with sepsis and at least one positive blood culture.²⁵ They analyzed 454 of 763 patients with sepsis and stratified the population between those on statins (>30 days prior to admission) who were continued on statins and those never on statins. There were 104 patients in the statin group (22.9%). Thirty day mortality was not different between groups (19.2% vs. 18.9%, respectively). The authors note that there was no evidence for toxicity from statins. Short term mortality was also not reduced in a study by Thomsen et al.²⁶ Mortality for hospitalized patients with bacteremia at 30 days was similar (20.0% vs. 21.6%, statin users and non-users). However mortality rates between days 31-180 were reduced in statin users (8.4% vs. 17.5%, adjusted mortality rate ratio 0.44; CI 0.24-0.80).

In a retrospective study of patients with ALI, Kor et al. found that statins did not confer a survival benefit or reduce organ dysfunction.²⁷ There was a reduction in ICU length of stay, but this may have been attributable to lower disease severity in the statin group as SOFA scores were lower. Fernandez et al. analyzed 438 ICU patients receiving mechanical ventilation for more

than four days, 38 of whom received statins before and during their ICU stay.²⁸ Statin treated patients were older (72 vs. 62 years) and had higher APACHE II scores (21 vs. 17) and higher hospital mortality (61% vs. 42%). Higher mortality persisted after adjustment for APACHE II predicted risk. The authors concluded that statin use was a marker of higher disease severity, older age, and comorbidities and these factors were insufficiently considered in the APACHE II mortality predictors. Again, no toxicity from statins was reported.

1.5. Potential Mechanisms of Action of Statins in Sepsis

Statins are a class of lipid-modifying drugs which inhibit the HMG-CoA reductase. This enzyme catalyzes the conversion of hydroxymethylglutaryl-CoA to mevalonate, an early rate limiting step in cholesterol synthesis. Over the past decade, statins have been identified as potential immune modulators.²⁹⁻³⁴ The mechanisms of immune modulation are complex and are regarded as lipid independent as they are not related to lowering of LDL cholesterol. However, most of the immunomodulatory effects of statins are due to inhibition of HMG-CoA reductase and the subsequent downstream effects of inhibition of isoprenoid lipid production.³⁵ This leads to alterations in G-protein mediated signaling, alterations in adhesion molecules, and cell proliferation.³⁶ Most of these immunomodulatory effects can be reversed by mevalonate supplementation supporting the conclusion that HMG-CoA inhibition is the main immunomodulatory pathway by which statins act.^{37, 38} However, non-HMG-CoA mediated anti-inflammatory effects have been reported. For example, statins bind directly to leukocyte CD11a/CD18 and thus interfere directly with leukocyte binding to ICAM-1.³⁹ The cellular functions affected by inhibition of HMG-CoA reductase are ubiquitous and involve neutrophil, monocyte, lymphocyte, epithelial and endothelial cell biology.

Statins affect the production of many cytokines including IL-6, IL-8, TNF- α , monocyte chemoattractant protein-1 (MCP-1), and CRP.²⁹⁻³⁴ Statins alter neutrophil attachment to the endothelium by directly interfering with adhesion as noted above but also by down-regulating surface expression of P-selectin, CD11b, and CD18.⁴⁰⁻⁴² Statins also inhibit lymphocyte function antigen-1 mediated neutrophil adhesion, inhibit LPS induced expression of monocyte toll-like receptor 2 and 4, improve platelet function, inhibit fibrinolysis, and increase endothelial nitric oxide synthase activity.⁴³ Many of the inflammatory pathways modulated by statins are thought to be involved in the pathogenesis of sepsis and ALI.^{8, 44}

1.6. Animal and Human Studies of Statins in Experimental Sepsis

Several animal models of sepsis demonstrate that statin pretreatment improves survival, biomarkers of inflammation, and cardiac function (Tabulated in Appendix C). One study by Merx et al. demonstrated that treatment of mice with statins 6 and 18 hours *after* CLP improved cardiac function and survival time (23 vs. 37 hours; $p < 0.05$).⁴⁵ This effect was seen with multiple statins, suggesting a class effect. Pretreatment with simvastatin 18 hours before CLP improved cardiac function and hemodynamic status within 20 hours of CLP and extended survival from 28 to 108 hours.⁴⁶ Yasuda et al. demonstrated that pretreatment for 3 days with oral simvastatin increased survival three days post CLP from 26% to 73% and at post-op day 2 from 42% to 84%.⁴⁷

Short term statin treatment attenuated acute lung injury in a model using intestinal ischemia-reperfusion.⁴⁸ Reductions in both blood and BAL concentrations of IL-1, Il-6, and IFN- α and p-selectin were reported. Reduced lung wet/dry ratios and histological lung injury scores were also observed.

Randomized controlled studies and observational studies in sepsis and ALI demonstrate that statins can reduce inflammation in acute disorders over a period of days.^{23,24,49} Steiner et al. administered LPS intravenously after four doses of simvastatin 80 mg/day vs. placebo in healthy subjects and found blunted responses of monocyte tissue factor expression and CRP at 4 and 8 hours post infusion.⁴⁹ Niessner et al. pretreated human volunteers with high dose statins or placebo prior to administering intravenous lipopolysaccharide (LPS). A resultant inhibition of toll-like receptor 4 and 2 led to reduced plasma levels of TNF α and MCP-1 as early as 4 hours after LPS injection.⁴³ In a randomized controlled trial in healthy volunteers, pretreatment with 4 days of simvastatin attenuated bronchoalveolar lavage levels of IL-1 β , TNF α , myeloperoxidase, α -1 antitrypsin, and matrix metalloproteinases-7,8,9 six hours after IV LPS.⁵⁰ Plasma CRP was also reduced.

In additional human studies, discontinuation of statins upon hospital admission was associated with worse outcomes. In patients with sepsis, Kruger et al. noted increased mortality in patients in whom statins had been stopped.¹³ In a RCT of aspirin plus heparin versus aspirin plus tirofiban, Heeschen et al. noted that patients in whom statins were discontinued had higher combined non-fatal myocardial infarction and death rates than non-statin users. Both groups had higher rates than those continued on statins. These associations were observed as early as 72 hours following randomization.⁵¹ Spencer et al. demonstrated that statin removal resulted in higher in-hospital morbidity and mortality in patients presenting with acute coronary syndrome.⁵² Patients in whom statins were initiated at the time of the acute coronary syndrome also fared better than patients who never received statins. Two studies in surgical patients demonstrate worse outcomes when statin therapy was not restarted immediately post-operatively. Collard et al. reported higher mortality following coronary bypass surgery if statins were not restarted (OR 2.64 (95% CI: 1.32-5.26)).⁵³ Le Manach et al. reported that myocardial necrosis in vascular surgery patients was greater in patients when statin therapy was not restarted until post-operative day 4 (OR 2.9. CI: 1.6-5.5).⁵⁴ Schouten reported in 298 patients undergoing major vascular surgery missing statin doses for a median of 3 days post-operatively (70 patients) had a hazard ratio of 4.6 (95% CI 2.2-9.6) for troponin leak and a hazard ratio for a 30 day outcome combined variable of death, myocardial infarction or death of 7.5 (95% CI 2.8-20.1).⁵⁵

In summary, acute and chronic immunomodulatory effects of statins are potentially useful for the prevention and treatment of sepsis. While the bulk of observational human and animal studies examine pretreatment with statins, two small RCTs in normal humans suggest the onset of the beneficial effects for the treatment of sepsis may be brief. Finally, one animal study demonstrated benefit after experimental sepsis and two small RCTs showed promising results with acute administration of statins for patients presenting with sepsis.^{23,24,45}

1.7. Rationale for Selecting Rosuvastatin

The pleiotropic effect of statins appears to be a class effect. As outlined above and in Appendix C, the retrospective and prospective human studies have included multiple statins. Animal experiments show consistent effects regardless of choice of statin. However, in the context of human trials of the FDA approved statins, rosuvastatin has the best drug-drug interaction profile. This attribute not only will likely improve the safety of this agent but also reduced the number of exclusions we will need in order to avoid drug-drug interactions. Rosuvastatin is 10% less protein bound than atorvastatin or simvastatin and is 10-15% more bioavailable.³⁴ It is hydrophilic as opposed to the latter two lipophilic drugs. Its side effect profile is comparable to other statins (Appendix C). Less than 0.1% of patients receiving rosuvastatin developed a 10 fold increase in CK. Significant hepatic dysfunction or failure has not been reported in the observational trials to date.^{12-19, 21-28, 53} Preliminary data from an ALI study of 60 patients randomized to simvastatin 80 mg/day vs. placebo revealed no differences in AST, ALT or CK values between populations. Furthermore, the frequency of adverse events, serious adverse events and drug related adverse events were not different (personal communication, D. McAuley).

1.8. Rosuvastatin Pharmacokinetics and Dose Selection

Rosuvastatin is rapidly absorbed with peak levels at 3-5 hours post dosing with a half life of 10-20 hours. Concomitant use of food reduces the rate of absorption by 20% but does not impact AUC. Time of day of dosing has no impact. Antacids should be administered 6 hours before or after rosuvastatin to avoid impact.¹ Eighty-eight percent of this drug is bound by plasma proteins, mostly albumin. Only 10% of rosuvastatin is metabolized. It is primarily excreted in stool (90%). It is not cleared through a renal mechanism. However caution is noted in renal failure, as risk for rhabdomyolysis may be increased in this setting. Dosing should be reduced in renal failure for patients not receiving chronic renal replacement therapy.

Since the anti-inflammatory effect of statins appears to be a class effect we have chosen rosuvastatin because it appears to be safe and has the fewest drug interactions of the statins. It also has a 10-20 hour half life allowing for once per day dosing.

We have chosen a moderate dose of rosuvastatin (20 mg maintenance dose, with adjustments for Asian decent and renal failure not compensated by renal replacement therapy). However, given the uncertainty of absorption, hepatic uptake and elimination we will assess drug levels after 60 patients are enrolled and adjust dosing if necessary (see section 5.2).

1.9. Study Rationale

The purpose of this study is to assess the efficacy of statin therapy for patients with sepsis-induced ALI. By restricting the population to those we believe to have both infection and evidence for systemic inflammation (sepsis), this study targets a disease process and population that has been best studied in animal models, observational trials and two small RCTs. By focusing on sepsis-induced ALI we have selected a group that has a higher disease burden than sepsis alone and thus likely to have both increased mortality and an increased opportunity for benefit, including a reduction in the requirement for mechanical ventilation. We completed a

survey of patients with suspected or known infection, SIRS, and acute hypoxic respiratory failure admitted to ARDS Network ICUs and found that 18% of patients were receiving statins prior to admission. Less than one percent of patients received statins during their ICU stay. We also identified that 88% of patients with sepsis-induced respiratory failure had bilateral infiltrates and thus met the definition for ALI. Given that the mortality and ventilator days are significant in patients with sepsis-induced ALI, we believe there is real opportunity for improved clinical outcomes if the right interventional agent can be identified. In choosing mortality and VFDs as the primary and secondary outcomes, we will be able to detect changes in clinical outcomes that are important to patients and to society.

2. Objectives

2.1. Primary Objectives

To assess the efficacy and safety of rosuvastatin in patients with sepsis-induced ALI

2.2. Hypothesis

Rosuvastatin therapy will improve mortality in patients with sepsis-induced ALI.

3. End-Points

Analysis of the primary, secondary and other endpoints will be conducted on an intention-to-treat (as randomized) basis.

3.1. Primary Endpoint

The Primary efficacy measure is hospital mortality to day 60.

3.2. Secondary End Points

Ventilator Free Days or VFDs to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

3.3. Other Secondary Endpoints

1. Hospital mortality to day 28
2. Organ failure free days at day 14
3. ICU-free days at day 28
4. Hospital-free days at day 60
5. Increase in $\text{PaO}_2/\text{FiO}_2$ ratio and Oxygenation Index on study days 1-7

6. VTE at day 14
 - a) Documented by venous ultrasound, impedance plethysmography, contrast venography, ventilation-perfusion lung scan, CTPA/V, or pulmonary angiography
7. Composite end-point of myocardial infarction, bowel ischemia or ischemic stroke to day 28
8. Arrhythmias during ICU stay or day 14, whichever is first
9. Development of acute kidney injury
10. Changes in plasma concentrations of CRP from day 0 to day 6 and 14. Blood and urine will be reserved beyond study completion for additional biomarker studies.

The rationale for the primary and first secondary endpoint is given in section 1.9. VTE is an endpoint because statins have been reported to be associated with lower rates of VTE in ambulatory patients.⁵⁶ Cardiovascular endpoints are being assessed given the high prevalence of occult cardiovascular disease and the known benefits of statins in this population. The development of AKI is an endpoint as observational studies suggest statins prevent AKI.^{47, 57-64} CRP is a surrogate marker of systemic inflammation and is expected to be reduced by statins.

3.4. Definition of Organ Failure:

Organ failure days are defined according to the most abnormal vital sign or lab value for each calendar day, according to the Brussels Organ Failure Table using the clinically significant organ failure thresholds.⁶⁵ Patients will be followed for development of organ failures to death, hospital discharge or study day 14, whichever comes first. Each day a patient is alive and free of an organ failure will be scored as an organ failure-free day. Any day that a patient is alive and free of all 5 organ failures will represent days alive and free of all organ failure.

3.5. Focused Safety Analysis:

The incidence of elevations in CK > 10 times ULN, **AST > 8 times ULN**, and ALT > 8 times ULN measured on days 0, 1, 3, 6, 14, and 21 (additional CK on day 10).

4. Study Population and Enrollment

4.1. Number/Source/Screening

The trial will accrue a maximum of 1000 patients over a 2-3 year interval. Patients with sepsis-induced ALI will be recruited from intensive care units at NIH ARDS Network hospitals. Study coordinators will screen intensive care units daily to identify potential candidates for enrollment. Permission to approach patients and/or their families will be requested from the attending physicians. All patients meeting the inclusion criteria will be entered into a screening log. If the patient is not enrolled, the screening log will include information explaining why enrollment did not occur (exclusion criteria, attending physician denial, patient refusal, etc. see Appendix J for a listing of the deidentified data to be collected on screened, non-enrolled subjects).

4.2. Inclusion Criteria

1. Systemic inflammatory response syndrome (SIRS) defined as meeting at least 1 of the following 3 criteria for a systemic inflammatory response. One of the SIRS criteria must be either the WBC criteria (a) or the body temperature criteria (b) :
 - a. White blood cell count $>12,000$ or $<4,000$ or $>10\%$ band forms
 - b. Body temperature $>38^{\circ}\text{C}$ (any route) or $<36^{\circ}\text{C}$ (accepting core temperatures only; indwelling catheter, esophageal, rectal)
 - c. Heart rate (> 90 beats/min) or receiving medications that slow heart rate or paced rhythm
2. Suspected or proven infection: Sites of infection include thorax, urinary tract, abdomen, skin, sinuses, central venous catheters, and bacterial meningitis (Appendix A).
3. ALI as defined by acute onset of:
 - a. $\text{PaO}_2 / \text{FiO}_2 \leq 300$ (intubated). If altitude $> 1000\text{m}$, then $\text{PaO}_2 / \text{FiO}_2 \leq 300 \times (\text{PB}/760)$, and
 - b. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph, and
 - c. Requirement for positive pressure ventilation via an endotracheal tube, and
 - d. No clinical evidence of left atrial hypertension, or if measured, a Pulmonary Arterial Wedge Pressure (PAOP) less than or equal to 18 mm Hg. If a patient has a PAOP > 18 mmHg, then the other 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 patchy or diffuse opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (> 28 days). The findings of vascular redistribution, indistinct vessels, and indistinct cardiac borders are not considered “consistent with pulmonary edema”.

All ALI criteria (3a-d above) must occur within the same 24 hour period. The onset of ALI is when the last ALI criterion is met. Patients must be enrolled within 48 hours of ALI onset and no more than 7 days from the initiation of mechanical ventilation. SIRS criteria must occur within the 72 hours before ALI onset **and the 24 hours after ALI onset**. Information for determining when these time window criteria were met may come from either the Network hospital or a referring hospital reports.

4.3. Exclusion Criteria:

1. No consent/inability to obtain consent
2. Age less than 18 years
3. More than 7 days since initiation of mechanical ventilation (**Example: If day of randomization is day “zero”, date of current intubation cannot be prior to day “negative 7”**)
4. More than 48 hours since meeting ALI inclusion criteria

5. 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).
6. Unable to receive or unlikely to absorb enteral study drug (e.g. patients with partial or complete mechanical bowel obstruction, intestinal ischemia, infarction, and short bowel syndrome)
7. Rosuvastatin specific exclusions
 - a. Receiving a statin medication within 48 hours of randomization
 - b. Allergy or intolerance to statins
 - c. Physician insistence for the use or avoidance of statins during the ICU stay
 - d. CK, ALT or AST > 5 times the upper limit of normal (ULN) except in patients with elevated CK who have an identifiable cause of CK elevation other than statin therapy providing the CK levels have fallen at least 10 % in the two most recent measurements **and** are less than 10 times ULN at randomization and the patient had not received any statins in the 30 days prior to enrollment (**Example:** A patient with staphylococcal sepsis has a CK of 3000 (10 times ULN). The next measurement is 2400 (8 times ULN). This patient would not be excluded for the elevated CK provided that no statins had been administered in the previous 30 days because the CK is now less than 10 times ULN, and the value has fallen more than 10% in the last two measurements).
 - i. If not available, a blood sample will be obtained after informed consent and results must be below protocol specified thresholds prior to randomization..
 - ii. CK, ALT and AST values obtained up to 24 hours prior to randomization are acceptable baseline values (e.g. Day zero) for both randomization and administration of the first dose of study.
 - e. Diagnosis of hypothyroidism and not on thyroid replacement therapy
 - f. Pregnancy or breast feeding
 - g. Receiving niacin, fenofibrate or cyclosporine, gemfibrozil, lopinavir, ritonavir, atazanavir, daptomycin while on study drug
8. Severe chronic liver disease (Child-Pugh Score 12-15)

Measure	1 point	2 points	3 points	Units
<i>Bilirubin (total)</i>	<34 (<2)	34-50 (2-3)	>50 (>3)	µmol/l (mg/dl)
<i>Serum Albumen</i>	>35	28-35	<28	g/l
<i>INR</i>	<1.7	1.71-2.20	> 2.20	<i>no unit</i>
<i>Ascites</i>	None	Suppressed with medication	Refractory	<i>no unit</i>
<i>Hepatic Encephalopathy</i>	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	<i>no unit</i>

9. Moribund patient not expected to survive 24 hours
10. Chronic respiratory failure defined as PaCO₂ > 60 mm Hg in the outpatient setting
11. Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing
12. Diffuse alveolar hemorrhage from vasculitis
13. Burns > 40% total body surface
14. Interstitial lung disease of severity sufficient to require continuous home oxygen therapy
15. Unwillingness or inability to utilize the ARDS network 6 ml/kg PBW ventilation protocol
16. Cardiac disease classified as NYHA class IV
17. Myocardial infarction in the previous 6 months
18. Intraparenchymal Central Nervous System (CNS) bleed within a month of randomization.

Rationale for Exclusions

Patients less than 18 years old are excluded because of limited clinical trial data with rosuvastatin in subjects younger than 18 years. Criteria 5, 8, 9, 10, 11, 14, 16, exclude patients unlikely to survive to the primary study endpoint or whose underlying condition or ventilator management complicates assessment of the secondary endpoint of VFDs. Criterion 7 excludes patients who are more likely to experience an adverse reaction or in whom it is more difficult to detect an adverse reaction to statins should one occur. Patients with diffuse alveolar hemorrhage (criterion 12) are excluded because the mechanism of lung injury is different from ALI due to infection. Patients with large burns (criterion 13) are also excluded as conservative fluid management may be contraindicated. Patients with advanced heart failure (criterion 16) are excluded because distinguishing ALI from pulmonary edema may be difficult and patients with both ALI and advanced CHF are unlikely to survive to the primary study endpoint.

4.4. Enrollment, Randomization, and Study Initiation Time Window

All ALI criteria (4.2.3a-d above) must occur within the same 24 hour period. The onset of ALI is when the last criterion is met. Patients must be enrolled within 48 hours of ALI onset and no more than 72 hours from the initiation of mechanical ventilation. SIRS criteria must occur within the 48 hours before and 24 hours after ALI onset. Information for determining when these time window criteria were met may come from either the Network hospital or a referring hospital reports. Following randomization, the low tidal volume protocol for mechanical ventilation and the fluid management strategy must be initiated within one and four hours respectively (if not already being utilized).

4.5. Informed Consent

Informed consent will be obtained from each patient or surrogate before enrollment in the trial. No study procedures will be conducted before obtaining informed consent.

4.6. Randomization

After informed consent is given, an assignment will be made by computer-generated randomization to administer either statin therapy or placebo. The randomization system will be based on Interactive Voice Response System (I.V.R.S.) technology or a web-based system. Each research coordinator will have a unique Personal Identification Number (PIN) which must be entered when using the system. A treatment assignment and individual subject identification number will be assigned. An emailed confirmation will follow to the study site. The randomization will be stratified by institution, and by shock at study entry to one of the two study arms.

4.7. Minorities and Women

Gender and racial patient subsets were considered by the NHLBI in selecting the Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate patient population contains representative proportions of minorities 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. Pregnant women will be excluded because of the lack of safety data for statin use during pregnancy.

5. Study Procedures

If a pregnancy test, ALT, AST or CK are not available before informed consent, blood or urine tests will be obtained after informed consent but before randomization to ensure eligibility. Patients excluded on the basis of tests obtained in this manner will not be included in the intent-to-treat population.

5.1. Statin or Placebo Administration

Rosuvastatin or placebo will be administered through an enteral feeding tube or administered orally following extubation when patients are able to safely take oral medications. The type and placement of the enteral feeding tube (nasogastric, nasoenteric, PEG, orogastric, oroenteric, etc.) and the ability to safely take oral medications will be determined by the patient's primary team. Study drug will be blinded with an identical appearing placebo.

The first study drug dose (rosuvastatin or placebo) will be administered within 4 hours of randomization as a loading dose of 40 mg.

1. Subsequent doses will be at 10 am daily (+/- 4 hours) starting on the next calendar day as a maintenance dose of 20 mg.
2. If for any reason a maintenance dose is not administered at the intended time, it may be administered subsequently but not more than 12 hours after the intended time of administration.

Should the time be > 12 hours since last scheduled dose, the patient will not receive a dose on that study day but will be given a loading dose on the next calendar day. Maintenance dosing will continue on subsequent days.

Daily doses will be reduced by 50% for patients with a creatinine level greater than or equal to 2.8 mg/dL who are not on renal replacement therapy. Loading doses will not be reduced.

Daily dosing:

- Each subject will receive full dose if last known creatinine value less than 2.8 mg/dL.
- Each subject will receive half dose if last known creatinine value greater than or equal to 2.8 mg/dL (unless receiving renal replacement therapy in which case a full dose will be given).

If used, antacids should be administered no closer than 6 hours before or after administering rosuvastatin to avoid affecting absorption of study drug.¹ The dosage need not be adjusted for ketoconazole, erythromycin, itraconazole, fluconazole, warfarin or digoxin.

5.2. Drug Level Specimens (venous blood)

The 40 mg loading dose and 20 mg maintenance dose are mid-range doses and were selected to quickly achieve and maintain plasma levels of rosuvastatin the range of 10-70 ng/ml. Plasma peak and trough levels of rosuvastatin will be obtained to determine the relationship, if any, of plasma levels to either the pleiotropic effects or the toxicities of statins. Trough levels will be drawn prior to the day 6 (+/- 2 day) dose. Peak levels will be drawn 3-5 hours after the dose.

5.3. Completion of Study Drug Administration

Patients will be considered to have completed the study drug administration portion of the study and the study drug will be stopped when one of the following conditions is met, whichever comes first:

1. 28 days after randomization or 3 days after ICU discharge (whichever comes first)
2. Discharge from study hospital
3. Death

Note: If patient is readmitted to the ICU while still on study drug before day 28, study drug should continue until three days after the next ICU discharge or day 28, whichever comes first. If the study drug administration has been completed and the patient is subsequently readmitted to the ICU, no further study drug should be administered.

The optimal duration of statin therapy for sepsis-induced ALI is unknown. The decision to examine a relatively long duration of therapy of up to 28 days was based on observational trials showing benefit with little or no toxicity when statins were continued throughout the ICU and hospital course. Furthermore, statin use in observational studies was of long duration prior to admission. The relative ease of once daily oral study drug administration was also considered in determining the duration of therapy.

5.4. Premature Withdrawal from Treatment

The study drug will be discontinued if a patient develops an increase in either CK > 10 times ULN, AST > 8 times ULN, or ALT > 8 times the ULN, or if patient develops an intraparenchymal CNS bleed. Study drug will also be discontinued if niacin, fenofibrate, cyclosporine, gemfibrozil, lopinavir, ritonavir, atazanavir, daptomycin are administered, or if primary care team or surrogate decision maker request. Data collection will continue on these patients, including the type and dose of any statin used as part of usual care following withdrawal of study drug.

5.5. Ventilator Procedures

Ventilator management, including weaning, will follow the modified ARDS Network lower tidal volume (6 ml/kg PBW) protocol (Appendix D).⁶⁶ If not already being utilized, this low tidal volume protocol for mechanical ventilation must be initiated within one hour of randomization. Since the time a patient achieves unassisted ventilation affects the secondary endpoint, VFDs, and because recent evidence-based consensus recommendations have identified a best practice for weaning, weaning strategy will also be controlled by protocol rules in accordance with these evidence-based recommendations. This will assure similar weaning methods and provide potential benefit to both study groups. This newer weaning strategy is a simplified version of the protocolized weaning strategy used in prior ARDS Network studies (see Appendix D).

5.6. On-Study Fluid Management

Fluid management during shock will not be prescribed. In subjects who are not in shock, a conservative fluid management approach will be required. This conservative fluid management approach will represent a simplification of the algorithm utilized in the ARDS Network FACTT study (see Appendix E).¹¹ If not already being utilized, this conservative fluid management approach must be initiated within four hours of randomization and continued until the subject has reached unassisted breathing (UAB) or study day 7, whichever occurs first.

6. Data Collection

6.1. Background Assessments

1. Demographic and Admission Data
2. Pertinent Medical History and Physical Examination
3. Height; gender, measured body weight (MBW); calculated predicted body weight (PBW).
4. Time on ventilator prior to enrollment
5. Type of Admission
 - a. Medical
 - b. Surgical scheduled
 - c. Surgical unscheduled
 - d. Trauma

6. Alcohol Use Disorders Identification Test (AUDIT) tool (Appendix I)
7. Acute or Chronic renal failure and use of dialysis
8. Survey of smoking history including:
 - Ever smoker (> 100 cigarettes in lifetime)?
 - If yes, current smoker?
 - Estimate of pack years (# packs per day) x (# years smoked)
 - If former smoker, when did the subject quit smoking?

6.2. Baseline Assessments

The following information will be recorded during the 24 hour interval preceding randomization. If more than one value is available for this 24 hour period, the value closest to the time of randomization will be recorded. If no values are available from the 24 hours prior to randomization, then values will be measured post randomization but prior to initiation of study drug.

1. APACHE III Score⁶⁷
2. CAM-ICU delirium screening assessment and RASS or RIKER sedation score at select hospitals
3. Vital Signs: Heart rate, systolic and diastolic blood pressure, body temperature, MAP, CVP.
4. Ventilator mode (including non-invasive ventilation), tidal volume FiO₂ and PEEP, inspiratory plateau pressure, and mean airway pressures. If on a pressure-cycling mode, peak pressure during inspiration will be assumed to be the plateau pressure.
5. Arterial PaO₂, PaCO₂, pH and SpO₂
6. Serum CK, AST and ALT
7. Date and time of all creatinine determinations in the 48 hours prior to enrollment.
8. Frontal Chest Radiograph – radiographic lung injury score (# of quadrants)
9. Vasopressors or inotropes (epinephrine, norepinephrine, phenylephrine, vasopressin, dopamine > 5 µg/kg/min, dobutamine, phosphodiesterase inhibitors)
10. Suspected or known site of infection
11. Plasma CRP level
12. Blood for DNA banking (Appendix H)
13. Blood for cytokines, mediators, and markers of inflammation. Plasma obtained from two, 10 ml EDTA anti-coagulated blood samples will be divided immediately after centrifugation into 4 equal 2 ml aliquots in specified tubes and frozen at -70⁰C.
14. Urine for cytokines, mediators and markers of inflammation. Urine obtained from the patients will be collected in an 8 ml sample tube and divided into 4 equal aliquots in specified tubes and frozen at -70⁰C.

6.3. Assessments after Enrollment

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

Reference Measurements

The following parameters will be measured and recorded using values closest in time to 8:00 A.M. on the days specified in the Time-Events schedule (Appendix F). The following conditions will be ensured prior to measurements: no endobronchial suctioning for 10 minutes; no invasive procedures or ventilator changes for 30 minutes. All vascular pressures will be zero-referenced to the mid-axillary line with the patient supine.

- 1) If receiving assisted ventilation record daily up to day 7:
 - a) Tidal volume, FiO₂, PEEP, inspiratory plateau pressure, and mean airway pressures
 - b) Pressure during inspiration if on a pressure targeted mode (PSV, PCV, etc).
 - c) Arterial PaO₂, PaCO₂, pH and SpO₂
- 2) CK, AST, ALT as in schedule of events (Appendix F)
- 3) Fluid intake and output
- 4) Vital signs: Heart rate, systolic and diastolic blood pressure, body temperature, CVP
- 5) Modified Brussels Score data days 0-14:
 - a) Vasopressor use (Y/N), worst systolic BP, creatinine, bilirubin, and platelet count for the day. The date and value of the highest creatinine between days 15-28
- 6) CAM-ICU delirium screening assessment and RASS or RIKER sedation score through ICU discharge or study day 28 at select hospitals
- 7) Presence of myopathy
 - 8) Frontal Chest Radiograph – Lung Injury Score
- 9) Occurrences of VTE, myocardial infarction, bowel ischemia, ischemic stroke and arrhythmias requiring treatment
- 10) Methylprednisolone equivalents greater than 20 mg
- 11) Daptomycin administration
- 12) Concomitant medications: niacin, fenofibrate, cyclosporine, gemfibrozil, lopinavir, ritonavir, or oral contraceptives. (Yes/No each day). The type and dose of statins prescribed as part of usual care if the study drug is withdrawn by the treating physician during the treatment period or prescribed after the treatment period will be recorded.
 - a) Study drug/placebo will be stopped should one of these medications be started.
- 13) Blood and urine for cytokines, mediators, and markers of inflammation. Plasma obtained from two, 10 ml EDTA anti-coagulated blood samples will be divided immediately after centrifugation into 4 equal 2 ml aliquots and frozen at -70°C . Urine obtained from the patients will be collected in an 8 ml sample tube and divided into 4 equal aliquots in specified tubes and frozen at -70°C . Specimens will be collected on days 3 and 6.
- 14) Plasma CRP levels on days 6 and 14
 - a) CRP will be followed as statins have been shown to acutely reduce CRP in septic and non-septic patients and could serve also serves as a biomarker of effect.²⁴
- 15) Blood for statin peak and trough levels (day 6, plus or minus one day)

Samples will be sent to a central repository to be stored (as described below). Samples will be identified by central repository accession numbers during shipment and storage in the central repository. In the future, when studies using the samples are approved, and are requested during the NHLBI *proprietary period*, the clinical coordinating center (CCC) will instruct the repository

to prepare the appropriate samples for shipment. The key relating the ARDSNet subject study ID number to the new specimen accession number will be kept at the CCC in a restricted access electronic file. The CCC will 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 studies will 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. Urine and plasma collected for this trial will be frozen and stored at a bio-repository for future research.

6.4 Assessments after Hospitalization

The following data, as well as vital status, will be collected at 6 and 12 months after ICU discharge (for the first 310 subjects enrolled into the SAILS trial **and then at select hospitals after the first 310 subjects enrolled**). 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 (National Death Index, 2000). 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 pilot tested to 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.*
2. Psychological Outcomes:
 - a. Depression and Anxiety: Hospital Anxiety and Depression Scale (14 questions) *Estimated administration time: 5 minutes*
 - b. Post-Traumatic Stress Disorder (PTSD): Impact of Events Scale—Revised (22 questions); *Estimated administration time: 3 minutes.*
3. Neurocognitive Outcomes:
 - a. Neurobehavioral Cognitive Status Examination.
 - b. Wechsler Memory Scale
 - c. Wechsler Adult Intelligence Scale
 - d. Controlled Oral Association Test
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*

6.5. Endpoint Determinations

1. Vital status at 60 days until discharged home on unassisted breathing.
2. Brussels Organ dysfunction failures at days 0-14
3. Time of initiation of unassisted breathing (assuming a patient achieves 48 consecutive hours of unassisted breathing)
4. Need for re-instituting assisted or mechanical ventilation after achieving 48 consecutive hours of unassisted breathing
5. Need for, timing, and duration of dialysis
6. Status 48 hours after initiation of unassisted breathing
7. ICU length of stay in calendar days including ICU days after readmission to ICU.
8. Hospital length of stay in calendar days and discharge disposition (home, other facility, with or without assisted ventilation)
9. For rosuvastatin toxicity:
 - a. CK >> 10 times ULN
 - b. ALT > 8 times ULN
 - c. AST > 8 times ULN

7. Statistical Considerations

7.1. Statistical Methods

At interim analyses hospital mortality to day 60 will be estimated using the Kaplan Meier estimate with patients who are discharged home considered as censored at day 61. At the final analyses where 60 day mortality will be known for everyone the binomial estimate will be used. The analysis will be stratified by co-enrolled treatment assignments if applicable. VFDs, ICU free days and hospital free days will be analyzed by analysis of variance, with treatment (active, placebo) and co-enrolled assignment if applicable. A secondary analysis will correct for the covariates for mortality developed from previous ARDS Network trials.

7.2. Early Stopping and Monitoring

Given the interest in statin therapy the monitoring boundaries were designed to have a relatively low probability of stopping for futility before 750 patients in order to avoid a trial which is equivocal as to whether or not statins are effective.

The maximum sample size will be 1000 patients. The study will be monitored using a flexible group sequential design that includes potential stops for both efficacy and futility. Efficacy stopping will be based on mortality alone while futility stopping will be based on both mortality and VFDs. The reported confidence intervals on the treatment difference will be adjusted for the group sequential design using the method of Jennison and Turnbull for interim analyses.⁷⁰

The alpha and beta spending boundaries have been developed using EAST (Cytel Inc). The table below gives the boundaries for the planned interim analyses occurring at 100, 250, 500 and 750 patients with a final analysis at 1000 patients. For analyses at these times these boundaries are extrapolated using cubic splines to have the same error spending functions.

When reviewing the table below, suppose that we are at the second interim analysis after 500 patients. The study would stop for efficacy if the difference in mortality between the active and the placebo arm was 11% in favor of the active arm. We would stop for futility if both the placebo arm had better mortality than the active arm (by a difference of 1.3%) and the placebo arm had more ventilator free days (by a difference in 0.33 days). In terms of p-values to stop for efficacy, the p-value for the mortality difference would need to be less than 0.001525 one sided. To stop for futility the p-value for both survival and ventilator free days would have to be greater than 0.6392 one sided.

Table 1: Efficacy and Futility Stopping Boundaries

Number of Patients	Efficacy Boundary		Futility Boundary		
	Difference in Mortality Active-Placebo	p-value one sided	Difference in Mortality Active-Placebo	Difference in VFD Active-Placebo	p-value one sided
100	-0.60	3.4E-14	.28	-7.33	0.9998
250	-0.26	1.84E-07	0.055	-1.44	0.8614
500	-0.11	0.001525	0.013	-0.33	0.6392
750	-0.069	0.009162	-0.013	0.33	0.3343
1000	-0.051	0.022001	-0.051	1.34	0.0220

With the sample size given the study has a 92% probability of rejecting the null hypothesis effect on mortality if the true difference in mortality is 9% (From 27% to 18%). The probability of rejecting the null hypothesis effect on VFDs is 92% assuming that the difference is 2.25 and the standard deviation of VFDs is 10.5.

Simulation of Stopping Bound Properties

Table 2 gives the results of 10,000 computer simulated clinical trials using the efficacy and futility boundaries described above, assuming that rosuvastatin truly reduces mortality by 9%

(from 27% to 18%). For example, if rosuvastatin is effect then we would have a 40% chance (12% +28%) of stopping on or before the 500 patient look.

Table 2: Simulations of SAILS under the assumption rosuvastatin is effective

Sample size at scheduled interim analysis	Percent of simulations that stop the trial for efficacy
100	
250	12%
500	28%
750	44%
1000	19%
Total %	91.68%

Table 3 gives the results of 10,000 computer simulated clinical trials assuming that rosuvastatin has no effect on mortality. For example, if rosuvastatin has no effect on either VFD or mortality then we would have a 25% chance of stopping on or before the 500 patient look.

Table 3: Simulations of SAILS under the assumption rosuvastatin is not effective (note: futility includes both VFD and Mortality)

Sample size at scheduled interim analysis	Percent of simulations that stop the trial for efficacy
100	0.0%
250	6%
500	19%
750	32%
1000	38%
Total %	96%

Subgroup Analyses from data at enrollment:

1. AUDIT score analysis
2. Shock presence or absence
3. Gender, Race, Ethnicity
4. Patients naïve to statins vs. those who had been on statins > 48 hours prior to enrollment.
5. Pneumonia - presence or absence
6. Direct vs. Indirect Lung Injury
7. Age by quartiles
8. CRP level at baseline by quartiles

8. Data Collection and Site Monitoring

8.1. Data Collection

Research coordinators will collect data and enter it directly into the web-based data entry system managed by the Clinical Coordinating Center or record on paper data forms. Data will be transferred to the Clinical Coordinating Center on a prescribed basis through a web-based data entry program.

8.2. Site Monitoring

Site visits will be performed on a regular basis by the Clinical Coordinating Center, to ensure that all regulatory requirements are met and to monitor the quality of the data collected. Records of Institutional Review Board approvals and patients' charts will be examined on a spot check basis to evaluate the accuracy of the data entered into the database.

9. Risk Assessment

9.1. Risks of Active Study Drug

Potential risks of study drug include hepatic injury, rhabdomyolysis, and interactions with other medications. To limit adverse drug interactions, we have chosen rosuvastatin which has the best drug-drug interaction profile of the currently FDA approved statins. Less than 0.1% of patients receiving rosuvastatin develop a 10 fold increase in CK. Significant rhabdomyolysis or hepatic dysfunction has not been reported in the observational trials of statins in patients with sepsis to date. Rosuvastatin side effect profile is comparable to other statins (Appendix B).

Preliminary data from a study of 60 patients with ALI randomized to simvastatin 80 mg/day versus placebo revealed no differences in AST, ALT or CK values between study groups. Furthermore, the frequency of adverse events, serious adverse events and drug related adverse events were not different (personal communication, D. McAuley).

9.2. Risks of Blood Draws

All patients will have blood drawn for research purposes. Most blood will be drawn through indwelling catheters. Risks of drawing blood percutaneously are uncommon and include bleeding and bruising.

9.3. 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 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 statins. For example, patients who have intolerances or allergies to statins, active hypothyroidism, and who are taking medications that may unfavorably interact with

statins are excluded. Furthermore, patients with rhabdomyolysis or hepatic injury are excluded as the detection of statin toxicity may be more difficult in such individuals. While these are considered relative contraindications in clinical care, for this trial they will be absolute contraindications.

Second, patients with ALI and ARDS may also have underlying conditions that would benefit from statins as part of usual clinical care, such as ischemic heart disease or hyperlipidemia. We will exclude patients if their attending physician plans to administer statins during the course of ALI for these or any other usual care indications.

Third, there are provisions in the protocol for reduction of the study drug dose for low creatinine clearance by reducing the dose when the serum creatinine is 2.8 mg/dl or greater and for anticipated genetic differences in hepatic drug clearance.

Fourth, levels in the first 60 patients will be evaluated by both the Steering Committee and the DSMB to assure that the achieved levels approximate the targeted range. The Steering Committee recommendation to either maintain or change the study drug dose will be reviewed by the DSMB during the protocol-specified 100 patient safety evaluation.

Finally, we will monitor for adverse effects to liver and muscle by monitoring CK and ALT. We will stop study medications if CK rises to more than 10 times ULN or ALT rises to more than 8 times ULN. Myopathy will be recorded in the case report forms, but study drug will not be stopped unless CK is 10 times ULN.

9.4. Potential Benefits

Most observational studies suggest a mortality benefit from prior or in-patient statin use after hospitalization for serious infections. None of the observational trials have reported significant statin-related toxicity. An animal model of acute lung injury and a human experiment with intravenous LPS demonstrate less lung injury with statins, which may result in shortening the time patients require mechanical ventilation.

9.5. Risks versus Benefits

Several observational and matched cohort studies suggest that statin therapy may reduce mortality in patients with sepsis. No toxicities related to statins were reported despite the critically ill nature of these patients. Preliminary data from a 60 patient RCT of patients with ALI using maximum dose simvastatin (80mg) for up to 14 days also did not reveal increased toxicity when compared to placebo (McAuley, personal and confidential communication). Specifically, liver function tests and creatinine kinase levels were similar in the simvastatin and placebo groups. Furthermore, a decrease in plateau pressure and improvement in SOFA scores were noted at day 14. Statins are well tolerated in non-septic hospitalized patients with acute stroke, acute coronary syndromes, and in patients undergoing major surgery.

Data from animal studies, human observational and matched case cohort trials, two small clinical studies in normal humans who received intravenous LPS, and one small RCT in patients with

ALI suggest a favorable risk to benefit profile for statins in sepsis-induced ALI and support the conduct of this Phase III trial.

10. Human 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.

10.1. Selection of Subjects

10.1.1. Equitable Selection of Subjects

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 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.

10.1.2. Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of a type of treatment for patients with ALI and ARDS. Due to the nature of these illnesses, the vast majority of these patients will have impaired decision-making capabilities. This study cannot be conducted if enrollment is limited to only those subjects with decision-making capacity. Potential benefits to participation in this study are increased survival and VFDs.

10.2. Informed Consent

Federal regulations 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. 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.

10.3. Continuing Consent

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

10.4. Identification of Surrogates

Many of the patients approached for participation in this research protocol will 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 legally authorized representative.

Regarding proxy consent, the existing federal research regulations ('the Common Rule') state 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 procedure(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 place⁷¹. 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.⁷²

10.5. 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 protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents more than minimal risks. Commentators and Research Ethics Commission have held the view that it is permissible to include incapable subjects in research that involves more than minimal risk as long as there is the potential for beneficial effects and if the research presents a balance of risks

and expected direct benefits *similar* to that available in the clinical setting.⁷³ 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."⁷⁴ 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..."⁷¹

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.

10.6. 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, and d) augmented consent processes. The specific nature of the additional safeguards will be left to the discretion of the individual IRBs.

10.7. 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. All computer entry and networking programs will be done with coded numbers only. All paper 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, the Federal Drug Administration or other authorized Federal Agencies, and the ARDS Clinical Coordinating Center.

11. Adverse Event Reporting

Investigators will determine daily if any clinical adverse experiences occur during the period from enrollment through study day 28 or hospital discharge, whichever occurs first. 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 course of treatment of patients with ALI. If clinically important and unexpected adverse experiences occur, they will be recorded on the adverse event case report form.

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 clinically important, untoward medical occurrence that is thought to be associated with the study drug or procedures, regardless of the “expectedness” of the event for the course of a patient with ALI.
3. The following will be reported as adverse events:
 - CK > 10 times ULN
 - ALT > 8 times ULN
 - AST > 8 times ULN
 - Intraparenchymal CNS bleed

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, 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. This would be in contrast to an isolated episode of transient hypoxemia (e.g. SpO₂ ~85%), related to positioning or suctioning. This latter event would not be considered unexpected by nature, severity or frequency.

Investigators will report all events that are **serious AND unexpected AND study-related**, as defined in Appendix G, to the Clinical Coordinating Center by phone, fax or email within 24 hours of becoming aware of event. 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 calendar days after the investigator discovers the event.

The Clinical Coordinating Center will report all serious, unexpected, and study-related adverse events to the DSMB, by email, or telephone, within 7 calendar days of the CCC being notified of the event. A written report will be sent to 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.

The Clinical Coordinating Center will also determine if the serious adverse event is unexpected for a statin. Unexpected for a statin is defined as any event not listed in the rosuvastatin package insert. If the Clinical Coordinating Center determines that any serious and study-related adverse event is unexpected for a statin, the FDA will be notified within 7 calendar days. Such events may also meet the definition of Unanticipated Problems as described below.

Investigators must also report Unanticipated Problems, regardless of severity, associated with the study drug or study procedures within 24 hours. An unanticipated problem is defined as follows:

Unanticipated Problem (UP): any incident, experience, or outcome that meets all of the following criteria:⁷⁵

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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13. APPENDICES

APPENDIX A: Guidelines for evidence of infection

1. **Infections of the thorax:**
 - a. Chest x-ray or CT scan showing a new or progressive infiltrate, consolidation, cavitation, collection, or pleural effusion, and a clinical presentation consistent with pneumonia or empyema
 - b. Pneumonia can be defined as the presence of new infiltrate (s), absence of a noninfectious explanation and either signs of SIRS as per protocol or purulent sputum production with an identifiable pathogen.
 - c. Aspiration Pneumonitis in the acute phase is not considered an infection. However, if SIRS persists > 24 hours after aspiration, then an infectious etiology can be presumed.

2. **Abdominal infection:**
 - a. Perforated viscus or ischemic bowel with either localized peritonitis
 - b. Peritoneal fluid with > 250 PMNs
 - c. Clinical signs of cholangitis or appendicitis
 - d. Clostridium difficile toxin positive with evidence of colon dilation
 - e. Suspicion of peritonitis by clinical examination only

3. **Skin or soft tissue infection:** Acute onset infection of the skin, such as erysipelas, or infection involving deeper soft tissue

4. **Bacterial meningitis:** cerebrospinal fluid analyses if available and a clinical presentation consistent with bacterial meningitis

5. **Urinary Tract:**
 - a. Positive test for granulocyte esterase or nitrate in urine, or a positive culture (defined as >10⁵ CFU/mL)
 - b. Urinalysis with increased WBC count or positive Gram stain

6. **Central Line infections:**
 - a. Catheter-related bloodstream infections (CR-BSIs) are defined as bacteremia/fungemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection (i.e., fever, chills, and/or hypotension), and no apparent source for the bloodstream infection except the catheter. The catheter must be in place for at least 48 hours prior to development of the bloodstream infection.

7. **Sinusitis**
 - a. Air fluid levels in sinus seen on CT scan

8. Use of antibiotics at time of consent (provided the antibiotics are not for prophylaxis) is considered evidence of suspected infection. Examples of prophylactic antibiotics include: pre-surgical incision, antibiotic for the prevention of pneumocystis jiroveci (aka carinii), herpes simplex, cytomegalovirus, and latent mycobacterial disease.

9. The following are not considered evidence of infection:

- b. Fever of unknown origin
- c. Blood cultures that are considered positive only because of the isolation of a likely contaminant organism
- d. Postoperative hypotension within 24 hours of incision and/or fever without a verified infectious focus.
- e. Leukocytosis alone in the presence of steroid usage is insufficient evidence of infection.
- f. Leukocytosis alone in the presence of connective tissue disorder is insufficient evidence of infection.

APPENDIX B: Skeletal Muscle and Liver Effects of Statins

1. Skeletal Muscle

- a. Rhabdomyolysis leading to acute renal failure is associated with a CK between 4500 and 10,000 IU/L.⁷⁶ We have chosen to use CK values greater than 10 times the ULN which will be < 3500. Values for CK upper limit of normal vary by lab, but do not exceed 350 at ARDS Network sites.
- b. Statin induced muscle disease is defined in most studies as muscle pain with CK levels > 10 times the ULN.⁷⁷ Routine measurement of CK levels before statin commencement is not required according to guidelines. Guidelines also suggest that there is no need to discontinue statin therapy in asymptomatic patients whose CK levels are elevated but not more than 10 times the upper range of normal⁷⁸ Statins rarely produce CK elevations above 10 times ULN⁷⁹.
- c. The incidence of statin induced muscle disease in cardiac patients is rare as are elevations in CK > 10 fold the ULN (1). The incidence of myopathy (CK > 10 fold ULN with symptoms) and rhabdomyolysis (CK > 1000 units/L with or without muscle symptoms) is rare. A study of 2265 patients randomized to simvastatin (80mg) or placebo following an acute coronary syndrome, found the incidence of myopathy to be 0.4% and rhabdomyolysis 0.13%.⁸⁰ Rosuvastatin treatment related myopathy (muscle weakness or myalgia with CK levels > 10 fold ULN) occur in 0.1% of patients receiving daily doses up to 40 mg.

2. Hepatotoxicity

- a. The incidence of elevated liver enzymes more than 3 times ULN is <1 % of patients on any statin. Acute hepatic failure is very rare with statin use. With lovastatin the incidence is 1/1.4 million patient-treatment years, which is equivalent to background incidence. It is believed that hepatic failure occurs in 0.5-1.0 per 100,000 patient years in statin users, which is also equivalent to the background incidence.⁸¹⁻⁸⁴

3. Comparative Toxicity of Rosuvastatin with Other Statins

- a. Dutch and US studies showed that the incidence of predefined hospitalized events with rosuvastatin did not differ from other statins as summarized in Table 1.^{85,86}

Table 1 Comparison of Rosuvastatin with other Statins

	Incident rate per 1000 person-years		
	Rosuvastatin	Other statins	No statin
US			
Rhabomyolysis	0.20	0.00	
Renal dysfunction	1.18	1.26	
Hepatic dysfunction	0.20	0.24	
In hosp death	0.78	1.32	
Netherlands			
Rhabomyolysis	0.00	0.00	0.01
Renal dysfunction	0.31	0.20	0.03
Hepatic dysfunction	0.00	0.11	0.06
All deaths	5.34	11.48	7.99

APPENDIX C: Pleiotropic Effects of Statins

*Summary statements in italics refer to studies focused on infectious provocateurs or ALI.
A table of equivalent statin doses follows.*

1. Cell culture studies

- a. Reduced human monocyte adhesion to endothelial cells⁸⁷
- b. Reduced PMA induction of NF- κ B⁸⁷
- c. Reduced human CD14⁺ monocyte adhesion to endothelial cells after stimulation by monocyte chemoattractant protein-1 (MCP-1)⁸⁸
- d. Reduced IFN- γ induced expression of MHC-II protein⁸⁹
- e. Reduced T-lymphocyte proliferation and IL-2 release in human endothelial cells pretreated with IFN- γ and atorvastatin⁸⁹
- f. Reduced expression of CD83, CD40, CD86, CCR7 and HLA-DR in human monocyte-derived dendritic cells incubated with statins and exposed to TNF- α or IL-1 β ⁹⁰
- g. Reduced expression of IFN- γ induced CD40 in cultured human vascular cells⁹¹
- h. Reduced activation, as measured by IL-6, IL-8 and MCP-1 of vascular cells by human recombinant CD40L⁹¹
- i. Reduced huCRP in incubated human hepatocytes exposed to peroxisome proliferators-activated receptor-alpha (PPAR α) activator⁹²
- j. Increased IL-8, MCP-1, TNF- α , IL-1 β have been reported in mouse monocytes cultured and exposed to LPS or immune complexes⁹³
- k. Inhibition of the induction of inducible nitric oxide synthetase (iNOS) and TNF- α , IL-1 β and IL-6 in astrocytes, microglia and macrophages stimulated with LPS or cytokines⁹⁴

2. Isolated human saphenous veins

- a. *Atorvastatin inhibited the three to four fold increased release of IL-8 and MCP-1 from human saphenous veins treated with low levels of endotoxin*⁹⁵
- b. Reduced expression of MCP-1 and NF- κ B activity induced by TNF- α in cultured vascular smooth muscle⁸⁹

3. Intact animals (mouse, rat)

- a. Reduced ischemia-reperfusion induced leukocyte adhesion through inhibition of lymphocyte function antigen-1 and not HMG-CoA reductase activity⁹⁶
- b. Reduction in huCRP in mice exposed to IL-1 β ⁹²
- c. *Reduced exotoxin-induced leukocyte rolling, adherence and transmigration of leukocytes after *S. aureus* α -Toxin was administered to rats pretreated (18 hrs) with statin*⁴⁰
- d. Reduced IL-4, IL-5 levels in BAL after IL-4, IL-5, IL-6 and IFN- γ in thoracic lymph nodes after allergen challenge⁹⁷

- e. Induced secretion of T_H2 cytokines Il-4, IL-5, Il-10 and TGF-β in experimental model of autoimmune encephalitis and promoted differentiation of T_H0 to T_H2 cells⁹⁸
- f. Reduced ischemia reperfusion injury in kidneys⁵⁷
- g. Reduction in creatinine levels with statin
- h. Improved GFR with statin
- i. Reduction in acute tubular necrosis with statin
- j. Reduced mitogen-activated protein kinase extracellular activated kinase-1/2 and transcription factors NF-κB and activator protein-1
- k. *Pretreatment with statin 18 and 3 hrs prior to cecal ligation and perforation⁴⁶. Active group had:*
 - i. *Preserved cardiac function and hemodynamic status*
 - ii. *Restored cardiac responsiveness to β-stimulation (dobutamine)*
 - iii. *Reduced monocyte adhesion to endothelium in septic mice*
 - iv. *Attenuated endothelial nitric oxide synthetase (eNOS) stimulation*
- l. *Pretreatment with statin at 12 and 1 hr before LPS injection⁹⁹*
 - i. *Reduced serum TNF-α, IL-1β at 2 hrs by 96 and 60% respectively*
 - ii. *Reduced serum nitrite and nitrate at 8 hrs by 44%*
 - iii. *Improved 7d survival from 23.7 to 73.3%*
- m. **Post-treatment** with a statin at 6 and 18 hrs after septic insult preserves cardiac function and hemodynamic status and prolongs survival (23 to 37 hours, $p<0.05$)⁴⁵
 - i. *Placebo mice survived 23±1.3 hours*
 - ii. *Atorvastatin mice survived 40±4.2 hours*
 - iii. *Simvastatin mice survived 37±3.6 hours*
 - iv. *Pravastatin 39±3.9hours*
- n. *Selective blockade of LFA-1 mediated adhesion and co-stimulation of lymphocytes³⁹*
- o. *Acute lung injury following intestinal ischemia-reperfusion injury⁴⁸*
 - i. *Pretreatment with statin for 3 days attenuates acute lung injury*
 - ii. *Reduced concentrations of IL-1, Il-6, IFN-α and p-selectin in blood and bronchoalveolar lavage fluid.*
 - iii. *Reduced lung Wet/Dry ratios, lung tissue malondialdehyde, and histologic injury score.*
- p. Pretreatment with high dose statin therapy 24 hours and at time of LPS introduction attenuated pulmonary vascular leak. Reductions in IL-6, TLR4, CCL12, 19 and 22 and increased levels of IL-16 were seen.¹⁰⁰

4. Human studies

- a. Reduced hs-CRP (-15%) after 48 hours of statin initiation¹⁰¹
- b. RCT (placebo v atorvastatin or atorvastatin dose finding)
 - i. Reduction in CRP 34% greater with statin at 16 wks in pts with unstable angina or non-q wave MI – (enhanced reductions in IL-6 at 16 weeks were not seen)¹⁰²

- ii. Reduction in CRP at 4 weeks (47% with atorvastatin, 25% with placebo, $p = 0.03$) in patients with stable and unstable angina¹⁰³
- iii. Reductions in hs-CRP with statin at low dose (10 mg/d) of 15% and high dose (80 mg/d) of 47% in patients with DM type II; hs-CRP increased 6.6% in placebo treated group¹⁰⁴
- c. RCT (alternate statin vs. atorvastatin)
 - i. Greater reductions in CRP (-36.4% vs. -5.2%; atorvastatin v pravastatin) in patients with CAD as measured at 18 months¹⁰⁵
 - ii. Greater reductions in median CRP at 12 and 36 weeks with atorvastatin compared to simvastatin in patients with hypercholesterolemia¹⁰⁶
 - iii. Increased endothelial-dependent vasodilation within 24 hrs after statin initiation¹⁰⁷
- d. Improved flow mediated vasodilation^{107,108} (17,51,55)
- e. Improved survival in lung transplant patients and reduced incidence of rejection, obliterative bronchiolitis, and infectious and neoplastic complications¹⁰⁹
- f. Induction of apoptosis of human lung fibroblasts in a dose- and time-dependent fashion, blocked by exogenous mevalonic acid¹¹⁰
- g. Infection-related mortality reduced in a three year prospective study that included 11,490 patients with atherosclerotic disease, 5698 of whom were statin users (0.9% v 4.1%, $p < 0.001$).¹¹¹ This represented a risk reduction of 78%.

5. Statin Equivalency Dosing Chart

Statins	Dose equivalents based on LDL lowering effect	
Rosuvastatin	10 mg	Astra Zeneca - Crestor
Atorvastatin	20 mg	Pfizer - Lipitor
Lovastatin	20 mg	Merck- Mevacor (generic)
Simvastatin	40 mg	Merck- Zocor (generic)
Pravastatin	80 mg	Bristol Myers - Pravacol (generic)

APPENDIX D: Ventilator Procedures

D.1. Ventilator Management

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 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 while participating in this trial^{112,113}. 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 (V_T , 6ml/kg predicted body weight, +/- 2ml/kg) may be used, provided the V_T target is monitored and adjusted appropriately. If airway pressure release ventilation (APRV) is used, 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. V_T Goal: 6 ml / kg predicted body weight.
3. Predicted body weight (PBW) is calculated from age, gender, and height (heel to crown) according to the following equations:
 - a. Males: $PBW \text{ (kg)} = 50 + 2.3 [\text{height (inches)} - 60]$
 - b. Females: $PBW \text{ (kg)} = 45.5 + 2.3 [\text{height (inches)} - 60]$
4. 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)
5. If Pplat > 30 cm H₂O, reduce V_T to 5 ml / kg and then to 4 ml / kg PBW if necessary to decrease Pplat to ≤ 30 cm H₂O.
6. If $V_T < 6$ ml/kg PBW and Pplat < 25 cm H₂O, raise V_T by 1 ml / kg PBW to a maximum of 6 ml/kg.
7. If "severe dyspnea" (more than 3 double breaths per 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 cm H₂O. If Pplat exceeds 30 cm H₂O with V_T of 7 or 8 ml/kg PBW, then revert to lower V_T and consider more sedation.
8. If pH < 7.15, V_T may be raised and Pplat limit suspended (not required).
9. Oxygenation target: 55 mm Hg < PaO₂ < 80 mm Hg or 88% < SpO₂ < 95%. When both PaO₂ and SpO₂ are available simultaneously, the PaO₂ criterion will take precedence.
10. Minimum PEEP = 5 cm H₂O
11. Adjust F_IO₂ or PEEP upward within 5 minutes if there are consistent measurements below the oxygenation target range
12. Adjust F_IO₂ or PEEP downward within 30 minutes if there are consistent measurements above the oxygenation target range.
13. There are no requirements for maintaining a specific PEEP to F_IO₂ ratio. The lower PEEP/higher F_IO₂ table represents a consensus approach developed by ARDS Network investigators in 1995. The higher PEEP/lower F_IO₂ table (ALVEOLI) yielded equivalent results in a randomized trial¹¹³ and would be acceptable and perhaps preferable in patients who appear to respond with a substantial increase in arterial oxygenation in the transition from lower to higher PEEP.

Lower PEEP/Higher F₁O₂ Treatment Group

F ₁ O 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 PEEP/Lower F₁O₂ Study Group

F ₁ O 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

Note: Levels of PEEP in these F₁O₂/ PEEP tables represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.

14. No specific rules for respiratory rate. It is recommended that the respiratory rate be increased in increments to a maximum set rate of 35 if pH < 7.30.
15. No specific rules about I:E. It is recommended that duration of Inspiration be ≤ duration of Expiration.
16. Bicarbonate is allowed (neither encouraged nor discouraged) if pH < 7.30.
17. Changes in more than one ventilator setting driven by measurements of PaO₂, pH, and Pplat may be performed simultaneously, if necessary.

D.2. Weaning

Commencement of Weaning (applicable to patients ventilated invasively or non-invasively)

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. F₁O₂ ≤ 0.40 and PEEP ≤ 8 cm H₂O or F₁O₂ ≤ 0.50 and PEEP = 5 cm H₂O
3. Values of both PEEP and F₁O₂ ≤ values from previous day (comparing Reference Measurement values, section 6.3)
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 ≥ 90 mm Hg without vasopressor support (≤ 5 mcg/kg/min dopamine or dobutamine will not be considered a vasopressor)

Spontaneous Breathing Trial Procedure and Assessment for Unassisted Breathing

If criteria 1-6 above are met, then initiate a trial of up to 120 minutes of spontaneous breathing with $F_{I}O_2 < 0.5$ using any of the following approaches:

1. Pressure support (PS) < 5 cm H₂O, PEEP < 5 cm H₂O
2. CPAP < 5 cm H₂O
3. T-piece
4. Tracheostomy mask

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

Monitor for tolerance using the following:

1. SpO₂ $\geq 90\%$ and / or PaO₂ ≥ 60 mm Hg
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 (defined as 2 or more of the following):
 - a. Heart rate $\geq 120\%$ of the 0600 rate (≤ 5 min at $> 120\%$ may be tolerated)
 - b. Marked use of accessory muscles
 - c. Abdominal paradox
 - d. Diaphoresis
 - e. Marked subjective dyspnea

If any of the goals a-e are not met, revert to previous ventilator settings or to PS greater than or equal to 10 cm H₂O with Positive End-expiratory Pressure and $F_{I}O_2 =$ previous settings and reassess for weaning the next morning. The patient will be reassessed for weaning (Section E2) the following day.

Decision to remove ventilatory support:

If tolerance criteria for spontaneous breathing trial (a-e above) are met for at least 30 minutes, the clinical team may decide to discontinue mechanical ventilation. However, the spontaneous breathing trial can continue for up to 120 minutes if tolerance remains in question.

D.3. Definition of Unassisted Breathing

1. Spontaneously breathing with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP ≤ 5 without PS or IMV assistance
5. Use of CPAP or BIPAP solely for sleep apnea management

D.4. Definition of Extubation

1. Removal of an oral or nasotracheal tube
2. If a patient receives a tracheostomy, the time of extubation is defined as the time when the patient achieves unassisted breathing as defined in section D.3

D.5. Completion of Ventilator Procedures

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

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

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

D.6. Removal from the Ventilator Management Protocol

Patients may be removed from the 6 ml/kg PBW tidal volume ventilation requirement if they develop neurologic conditions where hypercapnia would be contraindicated (e.g., intracranial bleeding, GCS < 8, cerebral edema, mass effect [midline shift on CT scan], papilledema, intracranial pressure monitoring, fixed pupils).

APPENDIX E: Conservative Fluid Management Approach

This fluid protocol captures the primary positive outcome of the FACTT trial on increasing ventilator free days. For patients with a CVC, this protocol should be initiated within four hours of randomization in enrolled patients, and continued until UAB or study day 7, 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 \geq 60 mmHg as fast as possible. Wean vasopressors 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.

For patients without a CVC, no fluid gain over the first 7 study days is recommended once patients' the blood pressure has stabilized. Stable blood pressure is defined as no requirement for either vasopressors or a fluid bolus to support blood pressure for 12 or more hours.

CVP (recommended)	PAOP (optional)	MAP \geq 60 mm Hg AND off vasopressors for \geq 12 hours	
		Average urine output < 0.5 ml/kg/hr	Average urine output \geq 0.5 ml/kg/hr
>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

§ Renal failure is defined as dialysis dependence, oliguria with serum creatinine > 3mg/dl, or oliguria with serum creatinine 0-3 with urinary indices indicative of acute renal failure.

[#] Recommended fluid bolus= 15 mL / kg 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.

APPENDIX F: Time-Events Schedule

Measurement/Event	Day 0	1	2	3	4	5	6	7	8	9	10	12	14	21	28	60/90
Demographics, History & Physical, Height, Weight	X															
AUDIT and smoking survey	X															
Etiology of ARDS, site of sepsis	X															
APACHE III Score	X															
Brussels Score [^]	X	X	X	X	X	X	X	X	X	X	X	X	X			
GCS	X							X					X			
Ventilator Parameters (including FiO ₂) *	X	X	X	X	X			X				X		X	X	
Arterial Blood Gases (PaO ₂ , PaCO ₂ , pH) and SpO ₂	X	A	A	A	A	A	A	A					A	A	A	
Vital signs *	X	X	X	X	X	X	X	X								
Blood Statin peak/trough level ^β							X									
Concomitant medications (Y/N)	X	X	X	X	X	X	X	X	X	X	X					
Presence of myopathy €																
I/Os	X	X	X	X	X	X	X	X								
Occurrences of MI, VTE, ischemic stroke, bowel ischemia €																
Episodes of arrhythmias ^Ω	X	X	X	X	X	X	X	X	X	X	X	X	X			
ALT ^β	X	X	A	X	A	A	X	A	A	A	A	A	X	X		
CK, ^β	X	X	A	X	A	A	X	A	A	A	X	A	X	X		
AST	X	X	A	X	A	A	X	A	A	A	A	A	X	X		
Chest X-ray (LIS)	X	A	A	A	A	A	A	A	A	A	A					
Plasma CRP levels ^β	X						X						X			
Blood for DNA	X															
Blood and Urine for markers of inflammation ^β	X			X			X									
Study Drug Administration Record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status															X	X

X = Required

A=When available

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

€ Data gathered until 72 hours after study drug is discontinued

[^]Daily for 14 days or until ICU discharge and the date and value of the highest creatinine between day 15 and 28

^Ω Data gathered until day 14 or ICU discharge, whichever occurs first

^β These may be obtained plus or minus two days except for baseline and day 1. Attempt to maintain spacing between labs and samples if obtaining on days other than those specified.

APPENDIX G: Adverse Events

Procedures for Reporting Adverse Events

1. 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.
2. Investigators will report all *serious, unexpected, AND study-related* adverse events to the Clinical Coordinating Center within 24 hours by fax, phone or email. 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 calendar days after the investigator discovers the event.
3. Definitions of Adverse Events
 - a. 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.
 - i. 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.
 - b. 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.
 - c. 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.
 - d. Organ failures or death related to ALI or ARDS or the patient's underlying condition that are systematically captured by the protocol should not be reported as adverse events *unless they are considered to be study related*.

APPENDIX H: Genetic Testing

Portions of the blood specimens as specified in this protocol will be used for genetic analyses 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 the extraction laboratory for seven years and then shipped to the central repository. A random number will identify samples 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 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 data base. All data released by the CCC for genetic studies will be linked to the specimen but will be de-identified.

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.

APPENDIX I: AUDIT Questionnaire
The Alcohol Use Disorders Identification Test ¹¹⁴

The Alcohol Consumption Questionnaire is important to administer because there is a common association between alcohol abuse and ALI ¹¹⁵. 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.

<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> <p style="text-align: right;"><input type="checkbox"/></p>	<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> <p style="text-align: right;"><input type="checkbox"/></p>
<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> <p style="text-align: right;"><input type="checkbox"/></p>	<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> <p style="text-align: right;"><input type="checkbox"/></p>
<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 2 and 3 = 0</i></p> <p style="text-align: right;"><input type="checkbox"/></p>	<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> <p style="text-align: right;"><input type="checkbox"/></p>
<p>4. How often during the last year have you found 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> <p style="text-align: right;"><input type="checkbox"/></p>	<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> <p style="text-align: right;"><input type="checkbox"/></p>
<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> <p style="text-align: right;"><input type="checkbox"/></p>	<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> <p style="text-align: right;"><input type="checkbox"/></p>
<p style="text-align: right;">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>	

APPENDIX J: 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 >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

APPENDIX K: Long Term Outcomes

K.1 Phone Surveys for Survivors from 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 LTO 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 (2)	3 item; <1 min.
Cognitive status	Orientation (Neurobehavioral Cognitive Status Examination)	- used in wide variety of medical patients - reliable and valid (29-31)	20 min. total time for all tests below(36)
	Logical Memory 1-2 (Wechsler Memory Scale)	- used in wide variety of medical patients - reliable & valid; age, sex& education norm (32, 33)	
	Digit Span (Wechsler Adult Intelligence Scale)	- used in wide variety of medical patients - reliable & valid; age, sex& education norm (32, 33)	
	Judgment (Neurobehavioral Cognitive Status Examination) Similarities (Wechsler Adult Intelligence Scale)	- used in wide variety of medical patients - reliable and valid(29; 30;32) - age, sex and education norms(33)	
	Controlled Oral Association Test (COWA) Hayling Sentence Completion Test	- used in wide variety of medical patients - reliable and valid (34, 35)	
Mental health			
a) Depression & General Anxiety	Hospital anxiety & depression (HAD) scale (13)	-Most widely used survey in medical patients(14) -Separate subscale for depression & anxiety -Reliable and validated in medical patients (14) -Highly correlated with psychiatric evaluation (13;15)	14 items; 5-4 minutes (2) Continuous
b) Post-traumatic stress disorder	Impact of Events Scale – Revised (IES-R) (16)	-IES is the most commonly used instrument for assessing PTSD in the ICU (15) -Revised version (IES-R) follows DSM-IV (17) criteria -Reliable and valid (16;18)	22 items; 3 minutes (2) Continuous
Health-related quality of life			
a) Generic	1. SF-36 version 2 (21)	-Most widely used instrument, esp in ALI (1-3;6-7) -Reliable and validated in ICU patients (23) -US population norms available (21)	36 items; 6 minutes; Continuous
	2. EQ-5D (EuroQOL) (22)	-Feasible for patients with inattention& fatigue (6;22) -Recommended for use in ICU patients (5) -Provides utility estimate with US norms (24)	6 items; 2-1 minutes (2) Continuous

Physical function	Functional Performance Inventory - Short Form (FPI-SF)	-Developed in chronic pulmonary patients -Comprehensive, reliable and valid (11;12)	32 items; 5 4 minutes; Continuous
Return to work	Custom instrument	-Developed & used in large cohort of ALI survivors (2)	12 item; 2 min. Categorical
Health care utilization	University of Toronto ARDS Outcome study instrument (4)	-Developed and used in large longitudinal cohort of ALI survivors (4)	27 items; 8 2 minutes; Continuous

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

Administration of phone surveys will be centralized at 2 sites: Johns Hopkins and Intermountain Medical Center, 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.

K.2 Statistical Considerations for Short Term and Long Term Outcomes

There are two primary outcome measures for the study:

- the short-term outcome of daily delirium (measured by CAM-ICU) and
- the long-term outcome of cognition (measured by detailed cognitive surveys with the Hayling survey score as the primary outcome measure).

In addition, a number of secondary short-term and long-term outcomes will be analyzed. A number of dichotomous and continuous measures of long-term efficacy of the treatment will be analyzed.

Short term measures:

- 1) Primary outcome: Daily delirium during the ICU stay will be compared across treatment groups using a logistic regression model based on generalized estimating equations (GEE) with a single predictor variable (treatment group). The GEE approach will allow us to appropriately account for the within subject correlation in the observed daily delirium within a subject.
- 2) Secondary outcome: Any delirium during the ICU stay will be compared across treatment groups using a chi-square test.
- 3) Secondary outcome: Survival times will be compared for the treatment arms using both a chi-square test (survival vs. not) and a log rank test (comparing the distribution of survival times across the treatment arms).

Long-term outcome measures:

- 1) Primary outcome: Hayling (scaled) score
- 2) Secondary outcome: Logical Memory 1&2 scaled scores
- 3) Secondary outcome: Digit span scaled scores
- 4) Secondary outcome: Similarities scaled scores

For each of the long-term outcomes, treatment group comparisons ~~Each of the comparisons~~ we will be done based on the data collected at 6 months, and at 12 months follow up, respectively. We will compare the raw continuous measures in the groups of patients

available for the follow up (survivors only analysis) using Student's t-test. 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 to compare outcome measures across patients receiving the different treatment arms but who would have survived and were able to be contacted for either treatment arm. First the expected probabilities of survival and ability to contact are computed using logistic regression based on baseline covariate information of the subjects. Then comparisons of the outcome measures across treatment arms 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. This statistical approach depends on the assumption that conditional on the values of the baseline 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.

K.3 Citations for M1 (Choice of survey instruments)

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