Prospective, Randomized, Multi-Center Trial of
Pulmonary Artery Catheter (PAC) vs. Central Venous
Catheter (CVC) for Management of Acute Lung Injury
(ALI) and Acute Respiratory Distress Syndrome (ARDS).

and

Prospective, Randomized, Multi-Center Trial of "Fluid
Conservative" vs. "Fluid Liberal" Management of Acute
Lung Injury (ALI) and Acute Respiratory Distress
Syndrome (ARDS).

ARDS Clinical Network
ARDSNet Study #05, Version IIA
Footnotes, Version V

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Contents

Part I

Study Summary

- **Titles:** Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter (PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

    and

    Prospective, Randomized, Multi-Center Trial of "Fluid Conservative" vs. "Fluid Liberal" Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

- **Objectives:**

    1. To assess the safety and efficacy of PAC vs. CVC management in reducing mortality and morbidity in patients with ALI and ARDS.

    2. To assess the safety and efficacy of "fluid conservative" vs. "fluid liberal" management strategies in reducing mortality and morbidity in patients with ALI and ARDS.

- **Study Design:** Multi-center, prospective, randomized, controlled clinical trials. Patients will be randomized into each of the two trials simultaneously (factorial design).

    1. A maximum of about 1,000 patients will be enrolled.

    2. Patients will be treated with the specific fluid management strategy (to which they were randomized) for 7 days or until unassisted ventilation, whichever occurs first.

    3. Patients randomized to PAC will utilize this catheter for at least 3 days and up to 7 days (depending on protocol defined stability criteria) or until unassisted ventilation, whichever occurs first. If the PAC is discontinued according to protocol between day 3 and day 7, the fluid management strategy will continue (until day 7 or unassisted ventilation, whichever occurs first) and will be guided by the CVC.

4. Patients randomized to CVC will utilize this catheter for 7 days or until unassisted ventilation, whichever occurs first.

- **Sample Size/Interim Monitoring:**

  1. This study uses a 2x2 factorial design comparing the use of a liberal fluid management strategy and a conservative fluid management strategy and comparing the use of the PAC to the use of the CVC. The trial will accrue a total of about 1,000 patients (about 250 patients in each of the four groups) providing about 500 patients treated with PAC to be compared against about 500 patients treated with CVC and about 500 patients treated with a fluid liberal strategy to be compared against about 500 patients treated with a fluid conservative strategy. This provides 90% power to detect a difference of 10% (from 31% to 21%) in mortality at day 60 in the two primary comparisons using a two sided p=.05 significance level. The principal analysis will be intent-to-treat, based upon randomization assignment.

  2. Either comparison may be stopped independently if the difference between the mortality rates of the two treatments is greater than the O'Brien-Fleming boundary. We will also monitor for an interaction between the two factors using a Pocock boundary. The trial will be monitored after each 200 patients.

  3. The trial will also be monitored by the steering committee for feasibility. Feasibility parameters will include accrual, the ability to follow the fluid management protocols, separation of the groups based on fluid balance data, and the frequency that a PAC is placed in the group that is randomized to CVC ("crossover"). If any of these parameters indicate that the trial is not feasible, the trial will be modified or terminated.

- **Inclusion Criteria:**

  Acute Onset of:

  1. $PaO_2/FiO_2 \leq 300$. If altitude > 1000m, then $PaO_2/FiO_2 \leq 300$ x (PB/760).

  2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse , homogeneous, or asymmetric.

3. Requirement for positive pressure ventilation via endotracheal tube.

4. No clinical evidence of left atrial hypertension.

Criteria 1-4 must occur together within a 24-hour interval.

"Acute Onset" is defined as follows: the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must be $\leq$ 28 days at the time of randomization.

- **Exclusion Criteria:**

1. Absence of current intent or ability on the part of the treating physician(s) to obtain or continue central venous access (that could be used for either CVC or PAC monitoring) as part of regular care of this patient.

2. Unwillingness or inability to utilize the low tidal volume (6ml/kg PBW) ventilator management protocol.

3. Presence of a PAC at any time after onset of ALI (meeting of inclusion criteria 1-4).

4. > 48 hours since onset of ALI (meeting of inclusion criteria 1-4).

5. Age <13 years.

6. Burns > 40% body surface area.

7. 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).

8. Bone marrow transplantation.

9. Acute myocardial infarction within the last 30 days.

10. Severe chronic respiratory disease:
    (a) FEV_1 less than 20 ml/kg PBW (*e.g.*, 1.4 L for 70 kg), or
    (b) FEV_1/VC less than 50% predicted, or
    (c) Chronic hypercapnia ($PaCO_2$ greater than 45 mmHg) and/or chronic hypoxemia (PaO_2 < 55 mmHg) on FiO_2 = 0.21, or
    (d) Radiographic evidence of chronic over-inflation or chronic interstitial infiltration, or

(e) Hospitalization within the past six months for respiratory failure ($PaCO_2 > 50$ mmHg or $PaO_2 < 55$ mmHg or O_2-Sat $< 88\%$ on $FiO_2 = .21$).

(f) Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, *e.g.*, unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean > 40 mmHg), or ventilator dependency.

11. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre Syndrome, and myasthenia gravis.

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

13. Malignancy or other irreversible disease or condition for which 6 month mortality is estimated to be $\geq 50\%$.

14. Vasculitis with diffuse alveolar hemorrhage.

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

16. Renal failure requiring renal replacement therapy.

17. Severe, chronic liver disease (Child-Pugh Score of 10-15, see Appendix F).

18. Furosemide allergy.

19. Lung transplantation.

- **Enrollment and Study Initiation Time Window:** All patients must be randomized within 48 hours of meeting inclusion criterion for ALI (inclusion criteria 1-4). The last inclusion criterion may be met at either the Network hospital or a referring hospital. Following randomization, the low tidal volume protocol for mechanical ventilation must be initiated within one hour (if not already being utilized). The appropriate catheter (PAC or CVC, based upon randomization) must be in place within four hours of randomization. Finally, initiation of the fluid management protocol (fluid liberal or fluid conservative, based upon randomization) must begin within two hours of the time of placement of the PAC or CVC.

- **Efficacy:** The primary efficacy variable is mortality prior to hospital discharge to 60 days. The major secondary efficacy variables include:

1) ventilator free days, which is the number of days of unassisted breathing after initiating spontaneous breathing to day 28, and 2) number of organ-failure-free days at day 28 after randomization. Several other secondary efficacy variables will be analyzed, as well, as outlined in the protocol.

Part II

Study Description

Prospective, Randomized, Multi-Center Trial of
Pulmonary Artery Catheter (PAC) vs. Central Venous
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Lung Injury (ALI) and Acute Respiratory Distress
Syndrome (ARDS).
Protocol for the NIH ARDS Network

1   BACKGROUND

The pulmonary arterial catheter (PAC) was introduced for clinical use in
1970 to provide diagnostic and monitoring information not available from
other clinical sources [1]. An amendment to the Food and Drug
Administration (FDA) act in 1976 charged the FDA with the responsibility
for insuring the safety and effectiveness of medical devices. The PAC has
been designated as a Class II device, one that requires special controls.
Approximately 1.5 million such catheters are sold in the United States
annually. Estimates indicate that 30% of PACs are used in cardiac surgery,
30% in cardiac catheterization laboratories and coronary care units, 25%
in high risk surgery and trauma, and 15% in medical intensive care units
(personal communication, Baxter Healthcare Corporation).

Observational studies and anecdotal reports of morbidity and mortality
associated with and directly related to the catheter [2]-[8] culminated in a
multi-institutional, case matched, statistically sophisticated study of 9
disease categories of patients by Connors et al. [9]. The fundamental
question raised by the Connors article, as well as by previous reports,
relates to "implied harm" that may be associated with use of the PAC.

Implied harm is defined as the excess morbidity and mortality found in these reports, but for which there is no discernible cause and effect relationship to the insertion or presence of the PAC. No prospective randomized studies directly relate increased morbidity and mortality to the insertion of the PAC, but a few prior studies infer that operational problems, errors in data interpretation, inappropriate therapeutic responses to catheter data, singly or in combination, result in no benefit to patients and may actually harm them [2]-[9].

The PAC provides a wealth of direct and indirect information about circulatory and respiratory systems and intravascular fluid volume over time. Specifically, the PAC allows measurement of central venous and pulmonary arterial pressure, pulmonary artery occlusion pressure (PAOP, or "wedge" pressure), mixed venous blood gases, and indicator-dilution cardiac output. Because the data are quantitative, more information, such as systemic and pulmonary vascular resistance, can be derived. The accuracy of these measurement is high in expert hands [10, 11], but is subject to proper placement of the catheter, calibration of transducers and user interpretation of wave forms and data [12, 13]. PAC data, properly interpreted, help to assess right and left ventricle function, intracardiac shunts, pulmonary ventilatory function and intra-vascular fluid status [14, 15]. Once the PAC is in place and is properly maintained, ongoing monitoring of these data may provide early information regarding trends toward improvement or deterioration [8] in response to therapeutic intervention [15]. No other monitoring system provides as much overall information for management of circulatory and respiratory inadequacy or for assessing intravascular fluid volume.

Direct morbidity and mortality associated with the PAC is related to complications from insertion, passage, and maintenance of the catheter. Such complications include pneumothorax, bleeding (hemothorax, etc.), arrhythmias, thromboembolism, pulmonary artery rupture, and infection [17, 20]. The incidence of these direct complications has been widely reported [17]; a consensus of experts estimates that serious complications occur in 0.1-0.5% of monitored surgical patients [15, 17, 18]. Ongoing observational studies are expected to better document the incidence of direct complications associated with the use of the PA catheter.

Morbidity and mortality may also result from misinterpretation or misapplication of data derived from the PAC. The insertion, use and

interpretation of data obtained from PACs requires special expertise that is not possessed by all health care professionals [12, 13]. Connors et al. [9] have also reported significant variability in the prevalence of PAC use across institutions even within patient disease groups that should be relatively homogenous.

Although there have been multiple calls for investigation [21, 22, 23], no definitive, randomized, prospective clinical trials designed to determine the safety and efficacy of the PAC in medical and surgical patients exist [15, 24]. The use of the PAC can be divided into diagnostic and management applications. In most cases, diagnostic applications require the catheter to be inserted for brief periods of time (less than 24 hours). The complication rates for these diagnostic studies are well documented and relate primarily to the insertion procedure or the catheter itself [12, 15]. On the other hand, the management issues related to the PAC are less well investigated.

The PAC catheter is used commonly in patients with acute lung injury (ALI) and its most severe subset, the acute respiratory distress syndrome (ARDS). ALI is a clinical problem of significant magnitude in terms of incidence (150,000 patients per year), mortality (30%-60% in most series) and cost (in part due to long stays in intensive care). In patients with ALI, the PAC has been employed widely both to confirm the diagnosis as well as to optimize hemodynamic management. However, there are no prospective data that establish the clinical risk/benefit ratio of use of the PAC in such patients. Although the data obtained from the PAC provides considerable physiologic information about the systemic and pulmonary derangements that occur in patients with ALI [25], it is not clear that such information improves therapy or clinical outcomes. Mitchell and co-workers [26] randomized 52 ARDS patients (already being managed with PAC) to either a extravascular lung water (EVLW) management (based on bedside indicator-dilution measurements) or a "routine" wedge pressure management group. The EVLW management strategy achieved both a lower overall net fluid balance and a lower extravascular lung water, and was associated with improved mortality and shorter ICU length of stay. This study suggests that achieving a lower fluid balance in ARDS patients is associated with improved clinical outcomes. In a retrospective study of 40 ARDS patients, those patients who experienced a reduction of wedge pressure of at least 25 percent during acute management (first 48 hours) were found to have better survival than those patients who did not

experience such a reduction in wedge pressure (75% vs. 29% survival, p < 0.02) [27].

Theoretically, measurement of the PAOP and cardiac output may make it possible for physicians to maintain pulmonary vascular pressures at a lower level, thus reducing the quantity of pulmonary edema that may develop in the presence of an increase in lung vascular permeability [25, 28]. Also, maintaining a lower pulmonary capillary pressure may prevent or minimize damage ("stress failure") to the capillary wall [29]. In normal animals, high pulmonary capillary pressure causes ultrastructural damage to the capillary walls, with a resulting "high permeability" (capillary leak) type of edema [29]. Of interest, a high concentration of leukotriene B_4 and inflammatory cells is also found in the bronchoalveolar lavage of these animals, suggesting the onset of an inflammatory process [29]. Such inflammation may be triggered by exposure of the highly reactive endothelial basement membrane [29].

Furthermore, the measurement of pulmonary arterial pressure and cardiac output may make it possible for physicians to administer vasoactive agents more skillfully in order to optimize cardiac output, maintain or improve renal function, and increase systemic blood pressure and blood flow to vital organs [25]. On the other hand, it is possible that measurement of central venous pressure alone using a central venous catheter (CVC) is adequate to optimize hemodynamics in patients with ALI. The issue can only be resolved with carefully designed prospective studies [30, 31]. Further, a well designed trial, complete with supporting clinical protocols, could be a model for other interventional studies of ALI specifically and critical care in general. Such a trial also has the advantage of systematically collecting data on the incidence of volume overload pulmonary edema in patients clinically thought to have ALI and evaluating how this information changes clinical management and outcome in prospective randomized trial.

2 Objectives

1. Primary Objectives:

   - Evaluate the impact of the pulmonary artery catheter (PAC) versus the central venous catheter (CVC) on mortality, ventilator-free days, and organ failure and economic outcomes

in patients with Acute Lung Injury (ALI).

- Evaluate the impact of a fluid conservative management strategy versus a fluid liberal management strategy on mortality, ventilator-free days, and organ failures in patients with Acute Lung Injury (ALI).

2. Primary Hypotheses:

- Use of the PAC will be associated with a reduction in 60-day mortality.
- Use of the fluid conservative management strategy will be associated with a reduction in 60-day mortality.

3. Secondary Hypotheses:

- Use of the PAC will significantly reduce the duration of assisted ventilation (as measured over 28 days).
  Use of the fluid conservative strategy will significantly reduce the duration of assisted ventilation (as measured over 28 days).
- Use of the PAC compared to that of the CVC will reduce the extent of multiple organ system dysfunction including liver function, hematologic function, gastrointestinal function (need for packed red cell transfusion), and an overall organ system dysfunction index (using the Brussels table) by day 7.
  Use of the fluid conservative strategy compared to that of the fluid liberal strategy will reduce the extent of multiple organ system dysfunction including liver function, hematologic function, gastrointestinal function (need for packed red cell transfusion), and an overall organ system dysfunction index (using the Brussels table) by day 7.
- Use of the PAC will be associated with a significant reduction in the lung injury score, the PaO_2/FiO_2 ratio, and/or the oxygenation index on days 1 through 7 after randomization compared to patients with a CVC.
  Use of the fluid conservative strategy will be associated with a significant reduction in the lung injury score, the PaO_2/FiO_2 ratio, and/or the oxygenation index on days 1 through 7 after randomization compared to patients with a fluid liberal strategy.
- The incidence of major complications (pneumothorax, catheter-related infection, and arrhythmias) will be the same for the PAC and the CVC.

3 Endpoints

3.1 Primary Endpoint

1. Mortality prior to hospital discharge to day 60.

3.2 Secondary Endpoints

1. Number of ventilator-free days (VFD) to day 28 after enrollment.

2. Number of ICU-free days at 7 and 28 days after enrollment.

3. Number of organ failure-free days at 7 and 28 days after enrollment.

4. Resource utilization (estimated from event-free days).

5. Number of complications associated with PAC and CVC (pneumothorax, catheter-related bacteremia or fungemia, and arrhythmias) while the catheters are in place.

6. Reduction of the PaO_2/FiO_2 ratio on days 1-7 after catheter insertion.

7. Improvement in Lung Injury Score on days 1-7 after catheter insertion.

8. Correlation between the pulmonary artery wedge pressure and the central venous pressure while the PAC and CVC are in place.

9. Changes in fluid therapy, use of vasoactive agents, and/or diuretics within the first 1-7 days after insertion of a PAC versus a CVC.

10. Correlation between PAC measure of cardiac output and clinical measures of skin temperature, capillary refill, and skin mottling and relationship to protocol driven interventions.

VFD to day 28 is defined as the number of days of unassisted breathing to day 28 after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be

counted from the end of the last period of assisted breathing to day 28 unless a period of assisted breathing was less than 24 hours and the purpose of assisted breathing was a surgical procedure. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0. Unassisted breathing is defined as breathing with face mask or nasal prong oxygen (or room air) following extubation, T-tube breathing, breathing with continuous positive airway pressure (CPAP $\leq$ 5 cm H_2O), or tracheotomy mask breathing.

Organ failure is defined as present on any date when the most abnormal vital signs/abnormal lab value meets the definition of clinically significant organ failure according to the Brussels Organ Failure Table. Patients will be followed for 7 days. Blood tests will be obtained on days 1-7 in order that the presence of clinically significant organ failure can be assessed. Each day a patient is alive and free of a given clinically significant organ failure will be scored as a failure-free day. Any day that a patient is alive and free of all 5 organ failures will represent days alive and free of all organ failure. Central nervous system dysfunction is evaluated using the Glasgow Coma Scale.

Bacteremia and fungemia are defined as isolation from one or more blood cultures of pathogenic bacteria, yeast or fungi with the exception of coagulase negative (or thermonuclease negative) Staphylococci or Corynebacteria. Coagulase negative Staphylococci or Corynebacterium bacteremia require the isolation of these organisms from at least two blood cultures drawn within 24 hours of each other containing the same organism in order to be deemed significant. Bacteremia and fungemia are considered catheter-related if they occur when the same organism is quantitatively cultured ($>$ 15 cfu) from a catheter tip (confirmed) or when, in the opinion of the patient's physician, the infection can only have been caused by the catheter (non-confirmed).

4   Study Population and Enrollment

4.1   Number/Source/Screening

Approximately 1,000 patients will be enrolled over a 3 year interval. Patients with ALI will be sought in the NIH ARDSNet intensive care

units. Study Coordinators at each site will visit each intensive care unit daily to identify potential candidates for enrollment. Permission to approach patients/families will be requested from attending physicians. All patients meeting the inclusion criteria will be entered on 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.).

4.2 Inclusion Criteria

Acute Onset of:

1. $PaO_2/FiO_2 < 300$. If altitude > 1000m, then $PaO_2/FiO_2 \leq 300$ x (B.P./760).

2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.

3. Requirement for positive pressure ventilation via endotracheal tube.

4. No clinical evidence of left atrial hypertension.

Criteria 1-4 must occur together within a 24-hour interval.

"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.

4.3 Exclusion Criteria

1. Absence of current intent or ability on the part of the treating physician(s) to obtain or continue central venous access (that could be used for either CVC or PAC monitoring) as part of regular care of this patient.

2. Unwillingness or inability to utilize the low tidal volume (6ml/kg PBW) ventilator management protocol.

3. Presence of a PAC at any time after onset of ALI (meeting of inclusion criteria 1-4).

4. > 48 hours since onset of ALI (meeting of inclusion criteria 1-4).

5. Age < 13 years.

6. Burns > 40% body surface area.

7. 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).

8. Bone marrow transplantation.

9. Acute myocardial infarction within the last 30 days.

10. Severe chronic respiratory disease:

   - FEV_1 less than 20 ml/kg PBW (*e.g.*, 1.4 L for 70 kg), or
   - FEV_1 /VC less than 50% predicted, or
   - Chronic hypercapnia ($PaCO_2$ greater than 45 mmHg) and/or chronic hypoxemia (PaO_2 < 55 mmHg) on FiO_2 = 0.21, or
   - Radiographic evidence of chronic over-inflation or chronic interstitial infiltration, or
   - Hospitalization within the past six months for respiratory failure ($PaCO_2$ > 50 mmHg or PaO_2 < 55 mmHg or O_2-Sat < 88% on FiO_2 = .21).
   - Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, *e.g.*, unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean PAP > 40 mmHg), or respirator dependency.

11. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre Syndrome, and myasthenia gravis.

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

13. Malignancy or other irreversible disease or condition for which 6 month mortality is estimated to be $\geq$ 50%.

14. Vasculitis with diffuse alveolar hemorrhage.

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

16. Renal failure requiring renal replacement therapy.

17. Severe, chronic liver disease (Child-Pugh Score of 10-15 See Appendix F).

18. Furosemide allergy.

19. Lung transplantation.

4.4   Enrollment and Study Initiation Time Window

All patients must be randomized within 48 hours of meeting inclusion criterion for ALI (inclusion criteria 1-4). The last inclusion criterion may be met at either the Network hospital or a referring hospital. Following randomization, the low tidal volume protocol for mechanical ventilation must be initiated within one hour (if not already being utilized). The appropriate catheter (PAC or CVC, based upon randomization) must be in place within four hours of randomization. Finally, initiation of the fluid management protocol (fluid liberal or fluid conservative, based upon randomization) must begin within two hours of the time of placement of the PAC or CVC.

4.5   Informed Consent

Informed consent will be obtained from each patient or surrogate prior to enrollment in the trial.

4.6   Randomization

After obtaining informed consent, the Clinical Coordinating Center will be called and an assignment will be made by computer-generated randomization to either the PAC or CVC and to either the fluid conservative or fluid liberal management strategies. The randomization

system will be based on Interactive Voice Response System (I.V.R.S.) technology. Each research coordinator will have a unique Personal Identification Number (PIN). He or she will call the system and be asked to supply the PIN. A treatment assignment and a patient ID number will be assigned. A faxed confirmation will follow to the site.

4.7   Minorities/Women

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

5   PROCEDURES

5.1   Insertion of the Catheter and Acquisition of Data

The patient will be randomized to receive either PAC (which includes the CVC port) or a CVC alone. At the time of enrollment, patients will have either central venous access (CVC but not PAC) or it will be the prior intent of the attending physician to attain such access. For patients with no central access at the time of enrollment, central access will be obtained via an internal jugular, subclavian, antecubital, or femoral vein (if the physician is willing to use this site for CVC or PAC). For patients with an existing central venous catheter who are randomized to PAC, the CVC will be changed over a wire to PAC for subsequent PAC placement. Alternatively, a PAC introducer may be placed using a new access site.

The type of CVC or PAC catheter used in this trial will be those already in clinical use in the study ICUs. The minimum requirement for PAC will be the availability of right atrial and distal PA ports as well as a capability to measure thermodilution cardiac output. PACs with continuous cardiac

output monitoring capabilities can be used. The type of catheters (number of ports, continuous cardiac output, etc.), antibiotic coating of catheter/introducer, the site of insertion, the date and duration of insertion will all be recorded on the case report form.

Catheters will be inserted using aseptic technique and full barrier precautions. Catheters will be pre-filled with heparinized saline solutions and the distal balloon will be tested with the injection of 1.5 cc of air followed by passive deflation. The PAC will then be inserted through the PAC introducer and the typical wave forms of the right atrium, right ventricle, pulmonary artery, and PAOP observed on the bed-side monitor. The balloon will then be passively deflated and reinflated to confirm the PAOP. An acceptable PAOP waveform should produce a tracing that is compatible with a left atrial wave form when assessed in reference to a simultaneously recorded electrocardiogram on a strip chart recording and the mean PAOP should be equal to or lower than the PA diastolic pressure. The insertion site will then be secured and dressed per local hospital policy. A chest radiograph will be performed immediately thereafter to confirm proper placement of the CVC and PAC. Location of the catheter tip with the balloon deflated will be as close to the pulmonic valve as possible to avoid technical problems.

Right atrial pressure, PA systolic pressure, PA diastolic pressure, and PAOP will all be measured in reference to the mid-thorax at the 4th intercostal space. Catheter transducer systems will be electronically zeroed to this reference point. Pressure measurements will be made on a 2-channel strip chart recorder that allows simultaneous display of the electrocardiogram and PA or RA wave form. The mean right atrial pressure and mean PAOP will be measured at end expiration. Cardiac output will be measured by thermodilution technique with either iced saline or room temperature saline as per the study ICU's procedures. Thermodilution cardiac outputs will be measured in triplicate and the average of the three injections will be recorded. No attempt will be made to time the injection to the respiratory cycle.

Hemodynamic measurements will be obtained at least every four hours by the nursing personnel in the study intensive care units and the strip chart recordings kept in the ICU. At a randomly selected time each day, the strip chart recording will be reviewed with a member of the study team to confirm accurate measurement of pressure and timing of respiration of the

respiratory cycle. Study personnel and the critical care nurses in the study ICUs will have the Pulmonary Artery Catheter and Clinical Outcomes (PACCO) educational materials and PACCO pre and post-tests available for training at each site.

Material will also be distributed to each site providing standard instructions for assessing capillary refill time, cutaneous "mottling" of the skin over the knees, and skin temperature at the knees.

5.2   Infection Monitoring

The catheter insertion site will be inspected daily. The presence of purulence alone, or erythema with one of the following: tenderness, and increased warmth, induration, lymphangitis, or probable thrombosed vein, will constitute local site inflammation and the catheter will be removed and a new insertion site selected. For patients with fever and other clinical signs of infection, the PAC introducer or the CVC introducer will be changed to a new line or introducer over a wire and the tip quantitatively cultured. For febrile patients with septic shock, the PAC or CVC will be removed and a new insertion site selected unless there is clearly a likely cause of septic shock other than the catheter.

5.3   Clinical Management

Hemodynamic management of patients in each of the four groups (PAC-fluid conservative; PAC-fluid liberal; CVC-fluid conservative; CVC-fluid liberal) will be conducted according to protocol, as provided in Appendix A.

5.4   Treatment Algorithm Validation

Compliance with the hemodynamic protocol instructions and safety of the protocol instructions will be monitored by the PAC committee daily for the first 60 patients (15 in each treatment cell) as part of the protocol evaluation process. During this period, the protocol rules may be refined through iterative application and evaluation in the ARDS Network sites.

The goals for this refinement phase will be to achieve $\sim$ 90% compliance with instructions with no safety concerns.

Protocol performance data will include percent compliance with the protocol instructions and adverse events. Summary data for the first 60 patients and the revised hemodynamic management protocols will be reviewed by the Steering Committee and the Data and Safety Monitoring Board. The iterative refinement process will continue during Steering Committee and DSMB review. The Steering Committee or the DSMB may ask that the detailed iterative refinement continue beyond sixty patients or recommend that the study proceed with the refined protocol.

5.5   Duration of Protocol

The fluid management strategy (fluid liberal or fluid conservative) will be carried out for 7 days from the time of randomization or until unassisted ventilation is achieved, whichever occurs first.

The PAC will be maintained for at least 3 days, and thereafter until a 24 hour period of hemodynamic stability occurs (defined as the absence of instructions for any of the following interventions by the fluid management strategy: fluid bolus, pressors, inotropes, diuretic) up to a maximum of 7 days or until unassisted ventilation is achieved, whichever occurs first. If the PAC is removed between day 3 and day 7 by the protocol defined stability criterion, a CVC will be maintained and will be utilized to continue the fluid management strategy (conservative vs. liberal) that the patient was initially randomized to.

The CVC will be maintained for 7 days or until unassisted ventilation is achieved, whichever occurs first.

For the purpose of determining the endpoint of protocol application, unassisted ventilation must be continuously achieved for at least 12 consecutive hours, or until discharge of the patient from the intensive care unit, whichever occurs first.

5.6 Schedule of Hemodynamic Management Events

The data that serves as "input" for the fluid management protocol will be obtained at least every 4 hours. In all patients, this includes blood pressure, urine output, clinical assessment of the effectiveness of the arterial circulation, and central venous pressure. In patients with PAC, this additionally includes measurement of pulmonary artery occlusion pressure and cardiac index. Based upon this data, the appropriate protocol "output" (maintenance fluid, bolus fluid, inotrope, diuretic, pressor) will be implemented.

If, prior to the next scheduled 4 hour assessment, a change in one of the data inputs occurs (*e.g.*, decrease in urine output), then the investigator shall have two options. First, it can be determined whether this change would cause a new output instruction, based upon the most recent available full set of data inputs (occlusion pressure, etc.) carried forward. If so, then a full set of data inputs must be obtained (unless less than 30 minutes have elapsed since a particular measurement was last obtained), and then the appropriate output instruction is implemented based upon this new full set of data. Alternatively, the investigator may elect to measure the data inputs at anytime, based upon clinical judgement. In any event, in all circumstances, output instructions will be carried out only based upon an updated full set of data inputs (each element obtained within 30 minutes or less of the output instruction).

5.7 Ventilator Management

(Ventilation management for all patients will be according to the 6 ml/kg protocol of ARDSNet Study 01 - ARMA - See Appendix C)

6 Data Collection

6.1 Background Assessments

1. Pregnancy test (serum or urine) for women of child-bearing potential

2. Demographic and admission data

3. Pertinent medical history and physical examination

4. Height; calculated predicted body weight (PBW)

5. Time on ventilator prior to enrollment

6. Type of admission

    (a) Medical
    (b) Surgical scheduled
    (c) Surgical unscheduled

7. Risk factors for ALI/ARDS (sepsis, aspiration, trauma, pneumonia, drug overdose, other)

8. Presence of following chronic diseases:

    (a) Metastatic cancer
    (b) Hematologic malignancy
    (c) AIDS

6.2 Baseline Assessments

1. Vital signs: heart rate (b/min), systemic systolic and diastolic blood pressure (mm Hg), body temperature ($^\circ$C)

2. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, plateau, peak, and mean airway pressures

3. Arterial PO_2, PCO_2, pH, and SpO_2

4. Central venous pressure

5. Mixed venous PO_2, PCO_2, pH, and SO_2 as well as central venous sample (simultaneous when PA inserted).

6. Urinary output (most recent 24 hour value) or mean hourly value for most recently available period

7. Serum electrolytes, BUN, creatinine, glucose, albumin, and total protein

8. Blood hematocrit/hemoglobin, WBC, and platelets

9. Glasgow Coma Score

10. Frontal chest radiograph

    (a) Radiographic lung injury score (# of quadrants)

    (b) Presence or absence of barotrauma

        • Pneumothoraces (R/L)
        • Pneumomediastinum
        • Pneumatoceles > 2 cm minimum diameter (R/L)
        • Subcutaneous emphysema

11. Administration of following medications:

    (a) Vasopressors

    (b) Inotropic agent

    (c) Diuretics

12. Presumed site of infection, if sepsis is the etiology of ALI/ARDS.

13. Results of special diagnostic studies performed to assess
    hemodynamic status (*e.g.*, cardiac echocardiogram)

14. Signs of the effectiveness of the arterial circulation (*e.g.*, capillary
    refill time, knee mottling, skin temperature, etc.).

15. Intake and output for 24 hours on that calendar date; intake to
    include types volumes of various fluids (*e.g.*, blood products, colloids,
    saline solutions

16. Evidence of anasarca (physical exam).

17. Blood for cytokines, mediators, and markers of lung injury. Plasma
    obtained from two, 10 ml EDTA anticoagulated blood samples will
    be divided immediately after centrifugation into 12 equal 1 ml
    aliquots in specified tubes and frozen at $-70°$C.

18. Admission interviews to determine health-related quality of life.

6.3 Assessments During Study

The following parameters will be measured and recorded daily from
4:00-10:00 am using the values closest to 8:00 am (except where indicated)
on days 1-7.

1. If receiving positive pressure ventilation:

   (a) Mode
   (b) PEEP level
   (c) Peak, plateau, and mean airway pressures
   (d) Minute ventilation

2. FiO_2

3. PaO_2, $PaCO_2$, pH, and SpO_2

4. Mixed venous PO_2, PCO_2, pH, SO_2 (not mandated, but entered if recorded)

5. Central venous PO_2 and SO_2 (not mandated, but entered if recorded)

6. Hemodynamic values (twice daily)

   (a) Systemic arterial systolic, diastolic, and mean pressure
   (b) Heart rate (b/min)
   (c) Central venous, pulmonary artery, PAOP, and end-diastolic pressures, and cardiac output

7. Intake in past 24 hours; intake to include types and volumes of various fluids (*e.g.* blood products, colloids, saline solutions).

8. Urine and other output in past 24 hours

9. Serum electrolytes, BUN, creatinine

10. Blood hemoglobin concentration

11. Administration of following:

    (a) Vasopressors
    (b) Inotropic agents

(c) Diuretics

12. Experimental treatment (*e.g.* nitric oxide)

13. Frontal chest radiograph

    (a) Lung injury score

    (b) Presence or absence of barotrauma

14. Brussels score

    (a) Worst PaO_2/FiO_2 for that date

    (b) Worst systolic blood pressure for that date

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

    (d) Use of vasopressors

    (e) Glasgow Coma Score

15. Results of special diagnostic studies performed to assess hemodynamic status in past 24 hours (echocardiogram, etc.)

16. Signs of effectiveness of the arterial circulation (capillary refill time, knee mottling, skin temperature, etc.)

17. Evidence of anasarca (physical exam)

18. Blood for cytokines, mediators, and markers of lung injury. Plasma obtained from two, 10 ml EDTA anticoagulated blood samples will be divided immediately after centrifugation into 12 equal 1 ml aliquots in specified tubes and frozen at $-70°C$. Blood will be collected on Days 0, 1, 3, and 7.

19. Vital status at 90 days if still in hospital.

20. Itemized billing records, discharge and post-discharge interviews at 2, 6, 9, and 12 months to determine use of healthcare services, health-related quality of life, and long-term survival. Post-discharge inteviews at 2, 6, and 12 months will assess cognitive function and mood.

In addition, the following will be recorded if they occur when a PAC or CVC is in place and up to 3 days thereafter:

1. Catheter-related fungemia or bacteremia

2. Arrhythmias

3. Venous thromboembolism in the veins adjacent to insertion of the CVC or PAC

7 Statistical Considerations

This study uses a 2x2 factorial design comparing the use of a liberal fluid management strategy and a conservative fluid management strategy and comparing the use of the PAC to the use of the CVC. The trial will accrue 250 patients in each of the four arms, which will give over 90% power to detect a difference of 10% (from 31% to 21%) in 60 day mortality at hospital discharge in the two primary comparisons using a two-sided p=.05 significance level.

This sample size consideration is based on the results of our earlier study (ARMA). This study found a 31.3% and 39.8% mortality at hospital discharge for 6 ml/kg and 12 ml/kg ventilation.

A full-scale economic analysis will be conducted according to the Panel on Cost-Effectiveness in Health and Medicine recommended standards.

7.1 Early Stopping and Monitoring

DSMB meetings will be scheduled when 200, 400, 600, and 800 patients have been treated. A two sided O'Brien-Fleming boundary [32] will be used to determine whether to stop each factor separately. If one factor stops the other randomization may continue. The stopping boundaries correspond to two sided p-values of 0.0000048, 0.0012, 0.0083, 0.0222, and 0.0409.

At each DSMB meeting a test for interaction will be performed. This test will be controlled for multiple comparisons using a Pocock boundary [33] in order to maximize the chance of early detection of a failure of our assumption that the effects of the two factors are additive. If a significant interaction is found it will be up to the DSMB to determine the best course of action. This may include stopping the trial or dropping one or

more of the arms. The Pocock boundary for a trial with five looks at the data would have a two sided p-value of 0.0158.

The trial will also be monitored by the steering committee for feasibility. Feasibility parameters will include: accrual, the ability to follow the fluid management protocol, separation of the groups based on fluid balance data and the frequency that a PAC is placed in the group that is randomized to CVP. If any of these parameters indicate that the trial is not feasible the trial will be modified or terminated.

The principal analysis will be by intent-to-treat, based upon randomization assignment. For example, patients who where randomized to receive a CVC, but who receive a PAC sometime during the defined treatment period, will be analyzed as having received the CVC (the treatment that they were randomized to). The rate and timing of "crossovers" will be monitored and will be a feasibility parameter at each interim analysis.

8 Risk Assessment

This study involves randomization of two separate (but potentially interacting) interventions: 1) PAC vs. CVC, and 2) fluid "conservative" strategy vs. fluid "liberal" management strategy. Each of the two randomizations carries with it potential risks (and potential offsetting benefits), and the possible interactions between the two trials may also have risk or benefit.

The trial of PAC vs. CVC essentially studies the incremental benefit or risk of adding the PAC catheter to the management of an ALI/ARDS patient who otherwise would be treated at least with CVC catheter (see exclusion criteria). Therefore, the risks of participating in this trial do not include those directly attributable to obtaining central venous access, such as pneumothorax, inadvertent arterial puncture, "baseline" infection rate of such catheters, etc. (The probably rare exception would be the patient who when randomized to receive the PAC would require a second central venous access for this purpose, due to a requirement for multiple ports for medication administration, etc.) Rather, the primary risk of participating in this trial relates to the incremental risk of having a PAC vs. having a CVC alone. This would include known "physical risks", such as cardiac

arrhythmias, pulmonary artery rupture, pulmonary infarction, etc., as well as physical risks of the PAC that may not yet be known. Furthermore, it is possible that the use of the PAC may lead to erroneous and adverse management, due either to inaccurate acquisition of the primary data (*e.g.*, pulmonary artery occlusion pressure, cardiac output). Conversely, the major risk of not utilizing the PAC is inadequate hemodynamic management that may occur due to the lack of potentially important information provided by the PAC, but not by the CVC (*e.g.*, pulmonary artery occlusion pressure, cardiac output, etc.).

The second trial consists of randomization to either a fluid "liberal" or "conservative" management strategy. Each of these strategies is thought to have potential benefit (such as lung protection in the fluid conservative group, and augmentation of renal and other organ perfusion in the fluid liberal group), but may also have risks (such as inadequate organ perfusion in the fluid conservative group and excessive pulmonary edema and delayed lung recovery in the fluid liberal group). The net balance of these potentially opposing risks and benefits is not known. Furthermore, the actual risks involved with the application of the specific fluid liberal and fluid conservative management strategies posses potential risks, in that these specific strategies have not been tested in patients previously. However, each of the strategies is felt to be clinically reasonable by the collective judgement of experts in the field. Conversely, there may be potential benefit to patients from the specific application of either one or both of these fluid management strategies (relative to "routine" care), in that each of these strategies has been carefully derived by a group of experts. During the early phase of the trial, and for as long as necessary, very close and specific attention will be paid to the safety and clinical "validity" of the specific fluid management strategies.

It is also recognized that there may be "interaction" between the two trials, which may cause benefit or risk, as well. For example, perhaps the fluid conservative management strategy is superior only when applied with the use of a PAC, but is hazardous when applied only with a CVC. In this hypothetical example, therefore, the patients randomized to receive the PAC with the fluid conservative strategy might have the best outcome among the four groups, whereas the patients randomized to CVC with the fluid conservative strategy might have the worst outcome of the four groups. The potential risks or benefits of such interactions between the two trials will be carefully monitored by the DSMB.

9 Data Collection and Site Monitoring

9.1 Data Collection

Each site will have one or more computers. The research coordinator will be responsible for maintaining a database using a custom designed database application. Data will be stored in this computer and transferred to the Clinical Coordinating Center on a prescribed basis.

9.2 Site Monitoring

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

10 Human Subjects

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

11   Adverse Event Reporting

The investigator will determine daily whether any clinical adverse
experiences have occurred through study day 21 or ICU discharge,
whichever occurs first. The investigator will evaluate any changes in
laboratory values and physical signs and make a determine as to
whether the change is clinically important and different from what is
expected in the course of treatment of patients with ALI or ARDS. If
clinically important and unexpected adverse experiences have
occurred they will be recorded on the adverse event case report form.

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

The Clinical Coordinating Center will report all serious, unexpected, and
study-related adverse events to the DSMB, by fax or telephone,
within 7 calendar days. 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.

12   Schedule of Events

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13 Appendices

A Composite Fluid Protocol Table

(Insert the Composite Protocol Table Here)

B Footnotes, Version V

A. Dobutamine:

1. Start at 5 mcg/kg/min and increase by 5 mcg/kg/min increments at 15 minute intervals until ineffective circulation reversed (CI $\geq$ 2.5 for PAC or fewer than 3 physical findings of ineffective circulation for CVP) or maximum dose of 20 mcg/kg/min reached.

2. Begin weaning 4 hours after ineffective circulation is reversed. Wean by $\geq$ 25% of the stabilizing dose at intervals of $\leq$ 4 hours to maintain effective circulation

3. If a patient is on dobutamine as a result of an earlier cell assignment, dobutamine should be ignored for the purpose of subsequent cell assignment, but should continue to be weaned per protocol.

B. Furosemide:

(If the protocol instructs the use of furosemide, and furosemide is unavailable, then bumetanide should be substituted for furosemide, with a dose equivalency ratio of 40: 1 (40mg of furosemide = 1 mg of bumetanide). As the protocol allows with furosemide, bumetanide can be delivered either via bolus or continuous infusion at the discretion of the physicians caring for the patient. If and when furosemide becomes available again, furosemide should be utilized to carry out protocol instructions.)

1. Withhold if:

   a. vasopressor or a fluid bolus given last 12 hours **OR**
   b. renal failure present (dialysis dependence)* **OR**
   c. oliguria with creatinine >3, **OR**
   d. oliguria with creatinine 0-3 and urinary studies indicative of acute renal failure.

2. For cells 3, 7, and 8:
   Begin continuous infusion of 3 mg/hour **OR** 20 mg bolus **OR** last known effective dose. Reassess urine output in 1 hour. Double dose *hourly* until urine output $\geq$ 0.5 ml/kg/hour **OR** maximum infusion of 24 mg/hour or maximum bolus of 160 mg

is reached. Discontinue furosemide if no response to maximum dose after 1 hour.

3. For cells 11, 15, 16, 18:
Begin continuous infusion of 3 mg/hour **OR** 20 mg bolus **OR** last known effective dose. Reassess in 4 hours; if still in a cell for which furosemide is indicated then:

    a. If intravascular pressure has declined by one or more pressure ranges (rows) repeat the same dose as before, and then reassess in 4 hours.

    b. If intravascular pressure range has not declined by one or more pressure ranges (rows), and if average urine output over the preceding four hours is less than or equal to 3ml/kg/hr, double the preceding dose and reassess in 4 hours. If average urine output over the preceding four hours is greater than 3ml/kg/hr, then give the same dose as before and reassess within four hours. Maximum daily infusion dose = 24 mg/hour x 12 hours (3 four hour cycles); maximum bolus does = 160 mg q 4 hours x 3 doses. If either the maximum daily infusion (24mg/hr x 12 hrs) or maximum bolus dose sequence (160 mg x 3) is given, then do not give additional furosemide doses for 12 hours following the end of the 12 hour infusion or for 12 hours after the third 160 mg bolus.

4. Repeat diuretic trial q 24 hours unless criteria in footnote B1 met. This period begins with administration of first protocol mandated dose of furosemide.

5. If at least one cell has passed that does **NOT** call for Lasix to be given, or at least 12 hours has passed from a sequence of maximum furosemide dosing, you can either start back at 20 mg, give the last known effective dose, or give any dose in between (as determined by the ICU team).

C. Fluid Bolus (Non-shock, except cell #19):

1. Administer 15 ml/kg PBW normal saline, Plasmalyte, or Ringer's lactate (rounded to the **NEAREST** 250 cc) or 1 unit of RBCs or 25 grams albumin (choice at discretion of physician) over ≤ 1 hour then reassess patient. For cells 5,6,9,10, reassess within one hour. For cells 13,14,19, reassess within four hours.

Administer up to 3 boluses over 24 hours if indicated by protocol. This 24 hour period begins with the first protocol-mandated non-shock bolus **OR** the first protocol-mandated bolus following shock reversal.

2. Additional fluid boluses are allowed at the discretion of the physician.

D. Fluid Bolus (Cell #19 only):

1. Withhold fluid bolus if: Cardiac index (CI) ≥ 4.5 **OR** $FiO_2 \geq 0.7$.

2. Use 15 ml/kg PBW normal saline, Plasmalyte, or Ringer's lactate (rounded to the **NEAREST** 250 cc) or 1 unit of RBCs or 25 grams albumin (physicians discretion) over ≤ 1 hour then reassess patient. Administer up to 3 boluses over 24 hours if indicated by protocol. This 24 hour period begins with the first protocol-mandated non-shock bolus **OR** the first protocol-mandated bolus following shock reversal.

3. Additional fluid boluses are allowed at the discretion of the physician.

E. KVO IV:

1. Also minimize as much as possible all other fluid volume (e.g., for delivery of antibiotics etc.), except as required for nutrition support.

F. Guidelines for Management of Shock: Shock is defined as a MAP $<$ 60 mmHg or a MAP > 60 while receiving vasopressors. Physicians have the choice of either fluid bolus and/or vasopressor therapy (in any order) as follows:

1. Fluid Bolus (Shock):
Use 15 ml/kg PBW normal saline, Plasmalyte, or Ringers (rounded to the **NEAREST** 250 cc) or 1 unit of RBCs or 25 grams albumin (physicians discretion) over ≤ 1 hour then reassess patient.

2. Vasopressor Therapy:
Choice of any single agent or any combination of the following:

a. Dopamine 5 mcg/kg/min, increase to a maximum of 25 mcg/kg/min.

b. Norepinephrine at 1 mcg/min, increase to a maximum of 100 mcg/min.

c. Epinephrine at 1 mcg/min, increase to a maximum of 20 mcg/min.

d. Phenylephrine at 10 mcg/min, increase to a maximum of 500 mcg/min.

3. Vasopressor Weaning (includes any dose of dopamine):

a. When MAP > 60 mmHg on a stable dose of vasopressor, begin reduction of the vasopressor by $\geq 25\%$ of the stabilizing dose at intervals of ≤ 4 hours to maintain MAP ≥ 60 mmHg.

b. Dopamine is considered "discontinued" for vasopressor use and cell assignment when it is weaned to ≤ 5 mcg/kg/min, but should continue to be weaned per protocol (footnote F.3.a. above).

G. Invalid PAOP

1. If a valid PAOP measurement cannot be obtained, use the pulmonary artery diastolic pressure to estimate the PAOP, based upon the most recently available relationship between PAOP and PADP, and assuming a stable arithmetic difference between the two values. For example, if the most recent prior valid measurements showed a PAOP = 10 and a PADP = 15, and the current PADP = 20 and a valid PAOP cannot be obtained, then assume a current PAOP = 15.

2. If neither a valid PAOP or PADP can be obtained, then utilize the current CVP value.

* Renal Failure

a. Dialysis dependence is defined as the period from the initiation of dialysis to the time that continuous dialysis is discontinued or to the time following the last session of intermittant dialysis.

b. During this period of dialysis dependence, urine output is considered to be adequate for the purposes of cell assignment.

C Ventilator Procedures

C.1 Volume Cycled Ventilation

C.1.1 Ventilator mode:

Volume Cycled Assist Control

C.1.2 Tidal Volume and Ventilator Rate Adjustments and Arterial pH Management.

1. Initial Ventilator Tidal Volume and Rate.
   Tidal Volume
   (In the following procedures, the term "tidal volume" refers to inspired volumes, corrected for gas compression in the ventilator conduits.)
   Initial tidal volumes will be set at 8 ml/kg predicted body weight (PBW) if pre-randomization tidal volume is > 8.1 ml/kg PBW. If pre-randomization tidal volume is 7.1 - 8.0 ml/kg PBW, then initial tidal volume will be 7 ml/kg PBW. If pre-randomization tidal volume is 6.1 - 7.0, initial tidal volume will be 6 ml/kg PBW. If pre-randomization tidal volume is ≤ 6.0 ml/kg PBW, initial tidal volume will be 6 ml/kg PBW. This will be reduced by 1 ml/kg PBW at intervals of ≤ 2 hours until tidal volume = 6 ml/kg PBW.

   Predicted body weight (PBW) is calculated from age, gender, and height (heel to crown) according to the following equations:

   Males: PBW (kg) = 50 + 2.3 [height (inches) - 60]
   Females: PBW (kg) = 45.5 + 2.3 [height (inches) - 60]

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

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

Arterial pH Goals

- Arterial pH Goal: $7.30 \leq \text{pH} \leq 7.45$.

- Arterial pH will be measured when clinically indicated.

- Management of alkalemia and acidemia may be according to the following rules:

  (a) Alkalemia (pH > 7.45): Decrease ventilator rate, if possible.

  (b) Mild acidemia ($7.15 \leq \text{pH} < 7.30$):
    - Increase ventilator rate up to maximum of 35 or until pH > 7.30 or $PaCO_2 < 25$ mm Hg.
    - If ventilator rate = 35 or $PaCO_2 < 25$, then bicarbonate infusion may be given.

  (c) Severe acidemia (pH < 7.15):
    - Increase ventilator rate to 35.
    - If ventilator rate = 35 and pH < 7.15 and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until pH $\geq$ 7.15 (under these conditions, the plateau pressure targets described below may be exceeded).

Plateau Pressure Goals: $\leq$ **30 cmH$_2$O.**

- Plateau pressures will be measured at a minimum frequency of q4 hours. Plateau pressures will also be measured and recorded 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients will be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause will be recorded. The pause will be removed for at least 6 breaths. The plateau pressure measurements will be replicated 3 times with at least 6 "non-plateau" breaths between measurements and the mean of the three values will be calculated. If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressure will be substituted.

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

- The minimum tidal volume will be 4 ml/kg PBW.

- Changes in the tidal volume, if indicated above, will be made within five minutes. Tidal volumes will be increased if plateau pressure $\ll$ target.

  (a) If tidal volume < 6 ml/kg and plateau pressure $\leq$ 25 cmH$_2$O, then tidal volume will be increased by 1 ml/kg until plateau pressure $\geq$ 25 cmH$_2$O or tidal volume = 6 ml/kg PBW.

  (b) If tidal volume< 8 ml/kg PBW AND Pplat < 30 cmH$_2$O AND airway pressure remains below the PEEP level during inspiration or the ventilator delivers frequent ($\geq$3/minute) double breaths because airway pressure falls below trigger threshold at the end of inspiration, then tidal volume will be increased by 1 ml/kg PBW. If these phenomena persist at tidal volume 8 ml/kg PBW or with Pplat $\geq$ 30 cm H$_2$O, additional sedation or neuromuscular blockade should be considered.

C.1.3   Inspiratory flow and I:E ratio.

Inspiratory flow rate will be adjusted to achieve I:E = 1:1.0 - 1:3.0

C.1.4   Oxygenation.

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

$$55 \text{ mmHg} \leq \text{PaO}_2 \leq 80 \text{ mmHg}$$

or

$$88\% \leq \text{SpO}_2\text{-sat} \leq 95\%$$

When both PaO$_2$ and SpO$_2$ are available simultaneously, the PaO$_2$ criterion will take precedence.
Oxygenation will be maintained in the target ranges using the following PEEP/FiO$_2$ combinations:

FiO$_2$	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	18-24

(Levels of PEEP in this FiO_2/PEEP scale represent levels set on the ventilator, not levels of total PEEP, auto-PEEP, or intrinsic PEEP.)

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

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

If a patient's PEEP/FiO_2 is not compatible with the PEEP/FiO_2 scale (e.g. immediately after randomization or after urgent changes in FiO_2 or PEEP in response to desaturations, hypotension, etc.), either PEEP or FiO_2 (or both) will be adjusted at intervals of 5-15 minutes until the PEEP/FiO_2 is compatible with the scale. The procedures for adjusting PEEP and FiO_2 to make them compatible with the scale are as follows:

- Arterial oxygenation higher than the target range:

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

- Arterial oxygenation lower than the target range:

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

- Arterial oxygenation within the target range:

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

If $PaO_2 < 55$ mmHg or $SpO_2 < 88\%$ and tidal volume = 4 ml/kg PBW (or the minimum tidal volume necessary for pH control, section C.1.4) and plateau pressure ≥ 30, then FiO_2 will be raised until $PaO_2 \geq 55$ or $SpO_2 \geq 88\%$ or $FiO_2 = 1.0$. If $PaO_2 < 55$ mm Hg or $SpO_2 < 88\%$ and $FiO_2 = 1.0$, PEEP will be raised by 2 cm H_2O increments to 24 cm H_2O. (In these circumstances, plateau pressure may exceed 30 cm H_2O).

Brief periods (≤ 5 minutes) of $SpO_2 < 88\%$ or $> 95\%$ may be tolerated without making changes in PEEP or FiO_2.

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

- If $FiO_2 = 1.0$ and PEEP = 25 cmH_2O and I:E =1.0 and $PaO_2 < 55$ or $SpO_2 < 88\%$, then a PEEP increase trial may be performed as follows:
    1. Increase PEEP by 2-5 cmH_2O increments to a maximum of 34 cmH_2O or until $PaO_2 \geq 55$ or $SpO_2 \geq 88\%$.
    2. If the PEEP increase trial is not effective within 4 hours (PaO_2 increased by at least 5 mmHg), then PEEP will be returned to 24 cmH_2O.

C.1.5   Simultaneous changes

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

C.2 Weaning

C.2.1 Commencement of Weaning

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

1. $\geq$ 12 hours since initial protocol ventilator changes, if any.

2. $FiO_2 \leq .40$.

3. Values of both PEEP and $FiO_2 \leq$ 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. Ventilator rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.

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

   If criteria 1-6 are met, weaning potential will be assessed during a CPAP trial of $\leq$ 5 minutes at CPAP = 5 cm H_2O and FiO_2 =.50. If respiratory rate remains $\leq$ 35/min during the 5-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the Pressure Support Wean Procedure (Section). If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the patient will resume A/C ventilation at the most recent settings. The patient will be reassessed for weaning the following day at 0600-1000. (If failure to maintain the respiratory rate $\leq$ 35 during the CPAP trial is attributed primarily to anxiety, then appropriate treatment for anxiety will be given and a second 5-minute CPAP trial initiated within 4 hours).

C.2.2   Initial Pressure Support (PS) Setting

(for patients with respiratory rate ≤ 35/min during 5-minute CPAP trial).

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

2. If respiratory rate ≤ 25/min during the 5-minute CPAP trial and tolerance criteria (section C.2.3, below) are met, then initiate PS = 5cm H_2O. If the respiratory rate = 26-35 during the 5-minute CPAP trial, then set initial PS = 20 cmH_2O and make adjustments to PS within 5 minutes if necessary to achieve respiratory rate = 26-35.

3. PEEP = 5 cmH_2O.

4. FiO_2 = .50.

C.2.3   Assessment for Tolerance

Patients will be assessed for tolerance using the following criteria:

1. Total respiratory rate < 35 (5 min at respiratory rate > 35 may be tolerated).

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

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

    (a) Heart rate greater than 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 goals 1, 2, or 3 are not met on initial set-up to PS, the ventilator mode will be changed back to A/C at back-up rate = most recent A/C settings and the patient will be reassessed the next morning.

C.2.4 Subsequent ventilator settings

1. Reduce PS level by 5 cm H_2O q1-3 hours. PS will not be decreased below 5 cmH_2O. No decreases in PS will be made after 1900.

2. If PS = 10, 15 or 20 cmH_2O is not tolerated, then return to A/C.

   (a) At 0600-1000 of the next day, return to last PS level tolerated and continue with step 1.

3. If PS level = 5 cmH_2O is not tolerated, increase PS by 5 cmH_2O to 10 cmH_2O and maintain until the following morning.

   (a) If a patient on PS=5 or 10 must go back to A/C for reasons other than intolerance to weaning (*e.g.*, surgical or other invasive procedures), the weaning sequence will be re-entered with section C.2.1.

4. If PS = 5 cm H_2O is tolerated for two or more hours (using tolerance criteria 1-3 above), assess for ability to sustain unassisted breathing (section C.2.5).

C.2.5 Assess for ability to sustain unassisted breathing.

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

1. $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mmHg.

2. Spontaneous tidal volume ≥ 4 ml/kg predicted body weight.

3. Respiratory Rate ≤ 35/min.

4. pH ≥ 7.30 if measured.

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

   (a) Heart rate > 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 criteria 1-5 are met for > 120 minutes,continue with unassisted breathing. If any criteria 1-5 are not met during the 120 minute trial, then resume PS ventilation at 5 cmH$_2$O and assess for tolerance (section C.2.3).

C.3 Definition of unassisted breathing.

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

(b) T-tube breathing, OR

(c) Tracheostomy mask breathing, OR

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

C.4 Completion of ventilator procedures.

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

(a) Death.

(b) Hospital discharge.

(c) 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 study hospital or > 28 days elapsed since enrollment.

C.5 Premature Withdrawal from Treatment.

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

D Adverse Events

1. Procedures for Reporting Adverse Events

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

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

2. Definitions of Adverse Events

   A *serious* adverse event is any event that is fatal or immediately life threatening, is permanently disabling, or severely incapacitating, or requires or prolongs inpatient hospitalization. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

   An *unexpected* event is any experience not identified by type, severity, or frequency in the current study protocol or an event that occurred unexpectedly in the course of treatment for Acute Lung Injury or ARDS.

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

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

E   Genetic Testing Procedures

Portions of the blood samples and buccal smears collected, processed, and stored as specified in this protocol may be used for genetic analyses in the future. Genetic analysis will involve, in part, the analysis of genomic DNA and will attempt to link genotypic information to the extensive phenotypic information measured as part of this study. A layered informed consent will be used to obtain the study subjects' consent for genetic testing as follows: 1) consent for genetic studies related to ARDS, or; 2) consent for future studies not necessarily related to ARDS, or 3) consent for genetic testing in both of these categories. The level of an individual's consent for testing (e.g. none, for ARDS studies, for future studies, or all studies) will be recorded in the Case Report Forms and stored in the Clinical Coordinating Center Database.

Samples will be sent to a laboratory for DNA extraction and then sent to a central repository to be stored (as described below). No DNA will be stored or retained at the extraction laboratory. Samples will be identified by their ARDSNet Study Numbers during shipment, extraction, and storage. 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. These samples will have their ARDSNet Study Numbers removed and will be re-labeled (anonymized) with a new number prior to shipment. The key relating the ARDSNet study number to the new specimen number will be kept at the CCC in a locked file. The CCC does not record nor store unique patient identifiers (such as initials, date of birth, hospital record numbers, addresses, phone numbers, etc.) in the data base.

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

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

(identified by the ARDSNet study number) be destroyed. Confirmation of destruction of samples will be sent to the CCC and forwarded to the clinical site only until the end of the network; after that, there will be no way to retrieve the samples since they will have been anonymized.

E.1   Sample Collection for genetic testing

1. 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.

2. Three buccal swabs will be collected in patients who have received blood products within the past 5 days or in whom the transfusion history is unknown. The purpose of obtaining buccal swabs (in addition to whole blood) in patients who have received blood products is to verify that the DNA isolated from whole blood is indeed tha patients DNA (*i.e.*, same as in buccal epithelial cells) and not that of the blood products donor. The brush will be twirled against the inner cheek for 30 seconds and each tube will be be labeled with a pre-printed ARDSNet label.

3. Shipments will be made at approximately monthly intervals to the DNA extraction laboratory.

F Exclusion Definitions

For exclusion criterion #17 (Chronic Liver Disease), calculate the
Child-Pugh Score. Patients with a history of chronic liver disease and
Child-Pugh Class C, which is defined as a total of 10-15 points on the
following scoring table [34], are to be excluded from the trial. The
Child-Pugh Score does not need to be calculated for patients with a
history of acute liver disease.

17. Liver Failure: Child-Pugh Class C, which is defined as a total of
    10-15 points on the following scoring table.

Points	Class
5-6	A
7-9	B
≥ 10	C

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

G   Economic Analysis of the Pulmonary Artery Catheter

G.1   Economic analysis component

The pulmonary artery catheter (PAC) is a commonly used device that provides hemodynamic data to guide care of the critically ill, such as patients with acute lung injury or the acute respiratory distress syndrome (ARDS/ALI). Clinicians believe PAC use improves decision-making and patient outcomes but evidence is lacking and recent data suggest the PAC may increase mortality as well as considerably increasing costs. In response, the NHLBI funded a large multicenter trial (Fluid And Catheter Treatment Trial (FACTT) (N01-HR-46054-46064)) where ARDS/ALI patients will be randomized to receive a PAC or the less invasive central venous catheter (CVC) and to receive a liberal or conservative fluid management protocol in response to data provided by the PAC or CVC. The primary end-point will be in-patient mortality.

This appendix describes a concurrent economic analysis of the PAC to complement FACTT. Our aims are to: 1.) compare differences between study arms in long-term survival, quality of life, and quality-adjusted survival; 2.) compare differences between study arms in acute care and long-term costs; 3.) calculate the cost-efficacy of PAC use (*i.e.*, the balance of costs and effects under the controlled environment of the FACTT trial), and; 4.) estimate cost-effectiveness under more "real-world" conditions and produce life-time cost-effectiveness ratios, thereby facilitating comparison of our results to other cost-effectiveness analyses.

The results of this adjunct to FACTT will substantially amplify the value of the data being collected and provide, for the first time, robust estimates from randomized data of the economic effects of the widespread application of this important technology.

We will achieve aims 1-3 by augmenting FACTT data collection with detailed information on hospital costs, extended survival follow-up for a minimum of one year, and post-discharge patient interviews to determine quality of life and resource use in the first year. We will achieve Aim 4 by constructing a microsimulation model first calibrated by results from FACTT and published data on life-expectancy and costs and then adjusted

to reflect the broader patient case-mix and clinical effects of PAC use in routine clinical practice. We will use patient-level data from the King County Lung Injury Project epidemiology study (NHLBI HL-96-014) to adjust case-mix and patient-level data from a large pragmatic trial of PAC use in the United Kingdom to adjust the clinical effects of PAC use.

These data are being collected and analyzed by the EA-PAC Core Coordinating Team located at the University of Pittsburgh; this component is being funded by AHRQ RO1 HS 11620-01. The group received it's IRB approval from the University of Pittsburgh to conduct this portion of the FACTT trial on August 22, 2001.

This section of the study will use the following tools:

1. Patient Contact Information

2. Patient EA-PAC Baseline Barthel ADL questionnaire (or)

3. Proxy EA-PAC Baseline Barthel ADL questionnaire

4. Patient EA-PAC 60-day Interview (or)

5. Proxy EA-PAC 60-day Inteview

6. Billing data

G.2   Cognitive and mood sequelae component

The ARDS Network is conducting a study on the long-term cognitive and mood complications experienced by ARDS survivors as part of FACTT. The study involves administering questionnaires over the phone at the end of the EA-PAC mental health quality of life interview (Appendix G1). This protocol was approved by the University of Pennsylvania IRB on January 24, 2002.

The phone interviews will be administered by the EA-PAC investigators in Pittsburgh, already IRB approved to conduct phone surveys as part of EA-PAC.

This part of the study will employ the following tools in addition to the ones used for the economic analysis section:

1. WMS-III: Digits Forward

2. WMS-III: Digits Backward

3. WMS-III: Letter-Number Sequencing

4. Controlled Oral Word Association Test

5. Hayling Sentence Completion Test

6. NCSE: Judgment

7. WAIS-III: Similarities

8. WMS-III: Logical Memory I

9. WAIS-III: Vocabulary

10. Zung Self-Rating Depression Scale

11. Beck Anxiety Index

12. PTSS-10