ARDS Network Investigators' Response to the October 7, 2002 OHRP Letter

March 12, 2003

A. Concerns, questions, and allegations regarding the ARMA trial (ARDSNet Study 01):

(1) OHRP is concerned that the requirements of 45CFR46.111(a)(1) and (2) were not satisfied for the ARMA trial. In particular, OHRP notes the following:

(a) Prior to designing the study and defining the experimental and control groups interventions, the ARDSNet investigators appear to have failed to define in a systematic manner the specific range and frequency of tidal volumes and plateau airway pressures that were used in routine clinical practice at the participating ARDSNet study sites.

We did not conduct a survey in our intensive care units (ICUs) to define the specific range and frequency of tidal volumes and plateau pressures used in routine clinical practice at the participating study sites because:

1. There was abundant evidence in published studies regarding the ventilator settings that physicians prescribed for ARDS patients, including tidal volumes and airway pressures. These studies were summarized in Tables 1, 2, and 3 of the August 19, 2002 letter from Gordon Bernard, M.D., chair of the NIH NHLBI ARDS Network to James Kiley, Ph.D., Director of the Division of Lung Diseases (Appendix A). Some of these studies included contributions from the ARDS Network investigators. ARDS Network investigators had conducted and published many other studies in ARDS, including several in which ventilator settings were the primary focus (cited in Section 1.1.1 of the ARDSNet Study 01 protocol). ARDS Network investigators' knowledge of their own practices and those of their colleagues were consistent with the published data. Moreover, the breadth of experience represented in the published studies exceeded the breadth of experience in our own ICUs. For example, over 1000 intensivists responded to a questionnaire regarding mechanical ventilation practices in ARDS[1]. Therefore, the published literature, validated by our knowledge of our own and our colleagues' practices, represented an abundant database with which to design the ARDSNet Study 01 protocols.

2. Published literature and knowledge of our own and our colleagues' practices indicated that selections of tidal volumes and inspiratory pressures in routine clinical practice were highly variable. The main reason for this variability was that two different schemes had been recommended to physicians for prioritizing competing clinical objectives[2-7]. However, there was no evidence from rigorously conducted clinical studies for the superiority of either of these approaches. The purpose of ARDSNet Study 01 was to determine which of these two approaches would yield better clinical outcomes. To accomplish this purpose, we designed two different mechanical ventilation protocols to represented the two different approaches for

prioritizing competing clinical objectives. For this purpose, a control group that represented routine care practices or the mean, median, or mode of routine care practices was neither necessary nor desirable. As explained in detail in our responses to issue A.(1)(b),

a) Both of the ARDSNet Study 01 protocols utilized ranges of tidal volumes and pressures that were consistent with contemporary opinion and routine clinical practices.
b) We had no reason to believe that the ARDSNet Study 01 protocols would be unsafe relative to routine clinical practices.
c) Numerous safeguards were incorporated into the trial procedures to ensure patient safety.
d) The ARDSNet Study 01 trial design is consistent with the highest standards for clinical trial design and also with the design of many other clinical trials in critical care and other areas of medicine.

We believe the requirements for 45 CFR 46.111(a)(1) and (2) were satisfied by our knowledge of routine care practices, and that 45 CFR 46.111(a)(1) and (2) did not require us to conduct a pre-study survey of the specific range of tidal volumes and plateau airway pressures used in routine clinical care at ARDSNet sites. The chart reviews required for responses to issues A(3) and A(8) of the OHRP letter of October 7, 2002 are related to this alleged failure to conduct such a survey before designing ARDSNet Study 01. *We maintain that such a survey was not necessary before designing ARDSNet Study 01, and it is not necessary now for the evaluation of a completed trial in which such a control group was neither required nor desirable*. We respectfully ask OHRP to comment on the data provided herein before requiring sites to proceed with the chart review outlined under A(3).

(b) The ARDSNet investigators appear to have failed to provide sufficient justification for designing a pivotal phase III clinical trial that (i) included only two experimental arms defined by target tidal volumes of 6 ml/kg of predicted (or ideal) body weight (with plateau pressures limited to 30 cm H_2O) and 12 ml/kg PBW(with plateau pressures limited to 50 cm H2O), and (ii) excluded a control arm managed with target tidal volumes somewhere in the range of 7-11 ml/kg PBW which may have encompassed the tidal volumes most frequently used in routine clinical practice at the time the study was initiated.

When ARDSNet Study 01 was designed in 1995, two different approaches had been recommended for setting tidal volumes and inspiratory pressures in ALI/ARDS patients. Each approach assigned different priorities to competing clinical objectives. One approach, which we called "traditional" because it had been recommended for a longer time, used generous tidal volumes with relatively high airway pressure[2, 5, 6]. The advantage of this approach was that it was more useful for maintaining gas exchange and breathing comfort, especially in patients with elevated dead space and intrapulmonary shunt[8-10]. However, some clinicians believed from studies in experimental models that this approach might cause lung injury from overdistention[11-14]. An alternative approach, which was recommended by some clinicians and researchers in the early 1990s [3, 4, 7], used lower tidal volumes with lower inspiratory pressures. In experimental models this "lower tidal volume" approach was associated with less

lung injury from overdistention [11, 14, 15]. Uncontrolled case series reports suggested that clinical outcomes in ALI/ARDS patients would be better with the lower tidal volume approach [3, 4]. Also, a preliminary report from a small randomized trial suggested that the lower tidal volume approach would yield better clinical outcomes [16]. However, the lower tidal volume approach frequently compromised the traditional goals of maintaining gas exchange and breathing comfort.

Physicians' interpretations of the data from experimental models and the very limited clinical data were highly variable. Because there was little evidence from rigorously conducted clinical studies for the superiority of either approach, physicians' practices varied greatly. This variability is apparent in the data cited in response A.(1)(a) above and the data shown below in Figures 1, 2, 3, 4, and 5. The survey of intensivists' practices by Carmichael et al [1] is

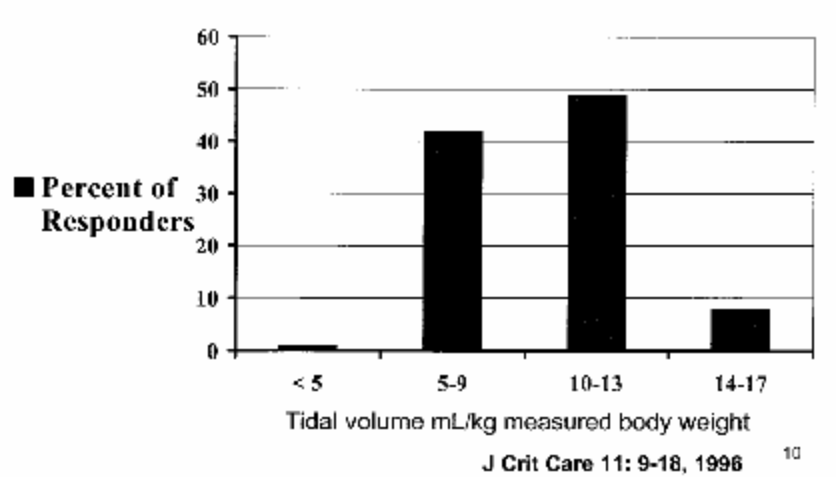

Figure 1: Survey of intensivists' practices by Carmichael et al [1]. Each bar represents the percent of survey respondents who indicated their choices for initial mechanical ventilation tidal volumes in patients with ALI/ARDS.

especially useful for this discussion because it reported intensivists' choices for *initial* tidal volumes in ALI/ARDS patients. The mainstream of these initial tidal volumes encompassed the broad range of 5-13 ml/kg measured body weight (equivalent to approximately 6-15 ml/kg predicted body weight, PBW). These initial tidal volumes would have been prescribed before information was available regarding any patient-specific factors, including inspiratory airway pressures. Therefore, *the broad range of initial tidal volumes reflected physicians' differing opinions regarding the importance of various competing clinical objectives.*

Considerable additional data demonstrate the great disparity in how physicians set tidal volumes and how they used (or did not use) inspiratory pressures to adjust tidal volumes.

1) In a clinical trial of surfactant therapy in ARDS published in 1996 [17], the range of physician-prescribed tidal volumes represented by the mean $\pm$ 2 standard deviations was 5–17 ml/kg measured body weight (Figure 2).

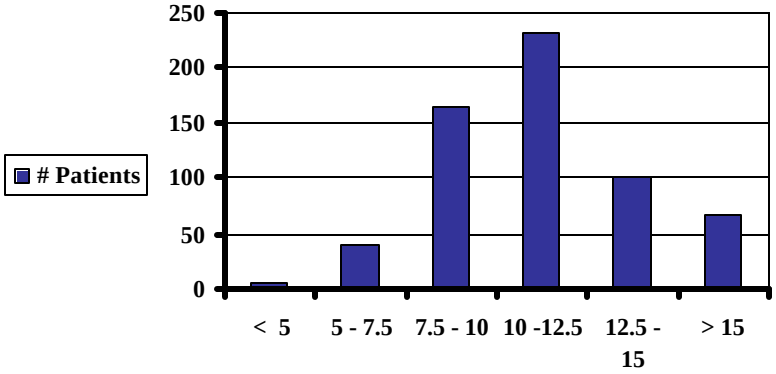

Figure 2: Tidal volumes prescribed by physicians in ALI/ARDS patients enrolled in a clinical trial of surfactant therapy. Values shown on the horizontal axis are tidal volumes in ml/kg measured body weight. In ARDSNet Study 01 [18], measured body weights exceeded predicted body weights by 20%. Therefore, to convert the tidal volumes shown here to ml/kg predicted body weight, multiply the values shown by 20%.

2) In a clinical trial of ibuprofen in sepsis conducted in the early-mid 1990s [19], in which most patients had acute lung injury, the range of physician-prescribed tidal volumes on the first study day represented by the mean $\pm$ 2 standard deviations was 5-16 ml/kg measured body weight.

3) In ARDSNet Study 01, 95% of the tidal volumes prescribed by physicians before patients were enrolled encompassed the range of 6-14 ml/kg PBW (Figure 3).

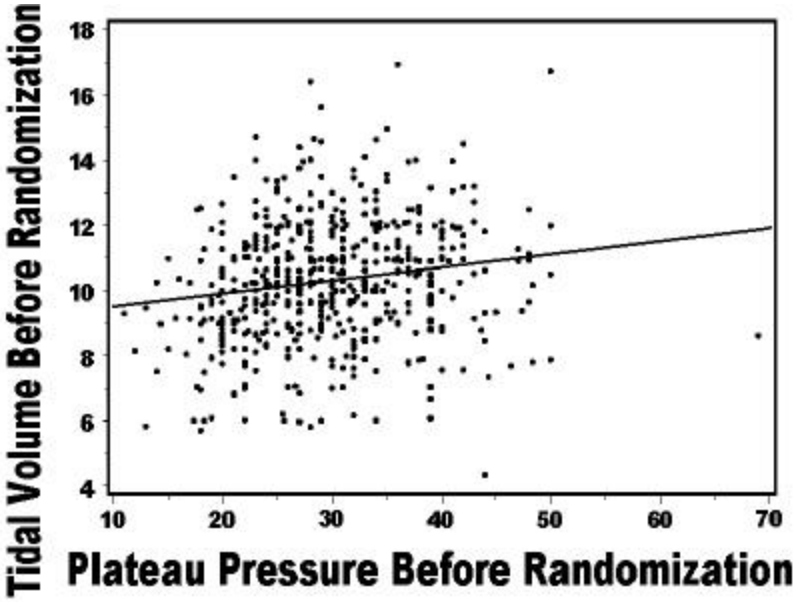

Figure 3: Baseline (physician-prescribed) tidal volumes (ml/kg PBW) and associated inspiratory plateau pressures (cm H_2O) in patients enrolled in ARDSNet Study 01 [18].

4) In an international survey of mechanical ventilation practices in ALI/ARDS patients conducted in 1998 [20], the range of physician-prescribed tidal volumes represented by the mean $\pm$ 2 standard deviations was 5-13 ml/kg measured body weight (equivalent to ~6-14 ml/kg PBW).

5) In a survey of mechanical ventilation practices in ALI/ARDS patients conducted in New England before the results of ARDSNet Study 01 were reported, the range of physician-prescribed tidal volumes represented by the mean $\pm$ 2 standard deviations was 7-18 ml/kg PBW (Appendix B).

6) In a survey of mechanical ventilation practices in ALI/ARDS patients conducted in King County, Washington from April, 1999-July, 2000, the range of physician-prescribed tidal volumes represented by the mean $\pm$ 2 standard deviations was 5-16 ml/kg PBW (Appendix C).

Thus, there was great variability in physician-prescribed tidal volumes (and associated inspiratory airway pressures) in ALI/ARDS patients. There are several reasons for these broad ranges in physician-prescribed tidal volumes: (1) There were differences of opinions among physicians regarding the risks and benefits of the two approaches to setting tidal volumes and inspiratory pressures. (2) In the absence of evidence from rigorously conducted clinical studies, physicians' practices are frequently influenced by factors that are external to specific patients [21]. These factors include most recent patient experiences and the strength of the opinions voiced by other members of the clinical team. (3) Tidal volumes are frequently set by individuals who lack experience and expertise in critical care. For example, ventilator settings are frequently prescribed by primary care physicians attending to their patients in intensive care units where there are no intensivists. (4) Tidal volumes are frequently set by respiratory therapists or residents during their ICU rotations. These practitioners may be supervised by attending physicians with more expertise, but intensivists are not available in many ICUs. Moreover, in the absence of clinical trials demonstrating the superiority of any approach, attending physicians frequently do not adjust the tidal volumes prescribed by less experienced clinicians if those tidal volumes are within the broad range of routine clinical practice.

Some of the variability in physician-prescribed tidal volumes could be attributed to deliberate adjustments by physicians responding to specific characteristics of individual patients. For example, elevated dead space (with associated elevations in $PaCO_2$ and decreases in arterial pH) in some patients could have triggered increases in tidal volumes by physicians who felt that it was important to maintain near-normal $PaCO_2$ and pH. Alternatively, low respiratory system compliance in some patients (with associated high inspiratory airway pressures) could have triggered decreases in tidal volumes by physicians who were more concerned about preventing lung injury from overdistention. However, several lines of evidence indicate that adjustments such as these (or in response to any other patient-specific factor) occurred rarely:

1) The ranges of tidal volumes in each of the studies and surveys summarized above are very similar to the range of *initial* tidal volumes that intensivists reported using in the survey by Carmichael et al [1]. One possible explanation for this observation is that some tidal volumes were raised and a similar number were lowered by similar amounts, making it appear as if there had been no changes. A more straight-forward and plausible explanation is that once tidal volumes were set, they were seldom adjusted in response to patient-specific factors.

2) In the ibuprofen in sepsis study [19], the mean $\pm$ 2 standard deviation range for physician-prescribed tidal volumes on day 3 of mechanical ventilation was 5 - 16 ml/kg measured body weight. This is essentially the same range as reported for the day 1 tidal volumes. This suggests that once tidal volumes were set, they were seldom adjusted in response to patient-dependent factors.

3) In the King County survey described above, the mean $\pm$ 2 standard deviation range for physician-prescribed tidal volumes on day 3 of mechanical ventilation was 5-17 ml/kg predicted body weight (Appendix C). This is essentially the same range as reported for the day 1 tidal volumes. This strongly suggests that once tidal volumes were set, they were seldom adjusted in relation to patient-dependent factors.

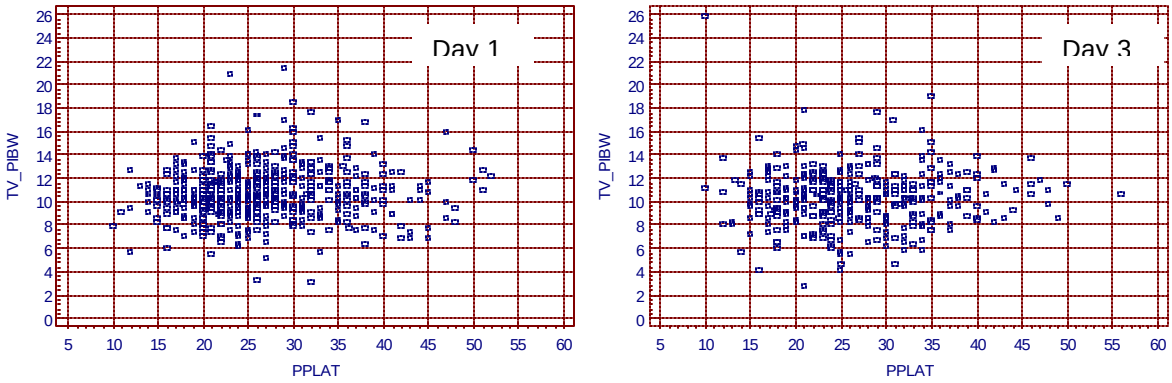

Figure 4: Physician-prescribed tidal volumes (in ml/kg predicted body weight) and associated inspiratory plateau pressures (cm H_2O) in ALI/ARDS patients in the King County Lung Injury Project. Left – Day 1 values. Right – Day 3 values.

4) In the King County survey (Appendix C), values of plateau pressure were recorded in only 68% of all ALI/ARDS patients. The absence of recorded plateau pressures suggests that many physicians were not concerned with this parameter, which is considered by many to be the best surrogate indicator for potential overdistention-induced lung injury.

5) In the King County survey (Appendix C), the frequency distributions of tidal volumes (Figure 4) are approximately the same across the entire wide range of plateau

pressures (~evenly split above and below 10.5 ml/kg PBW). These data strongly suggest that physicians were not concerned with plateau pressure, which is considered the best surrogate indicator for potential overdistention-induced lung injury.

6) In the survey of New England physicians' mechanical ventilation practices in ALI/ARDS patients (Appendix B), the frequency distribution of tidal volumes was approximately the same across the entire wide range of plateau pressures (~evenly split above and below 750 ml/kg). These data strongly suggest that physicians were not concerned with plateau pressure, which is considered the best surrogate indicator for potential overdistention-induced lung injury (Figure 5).

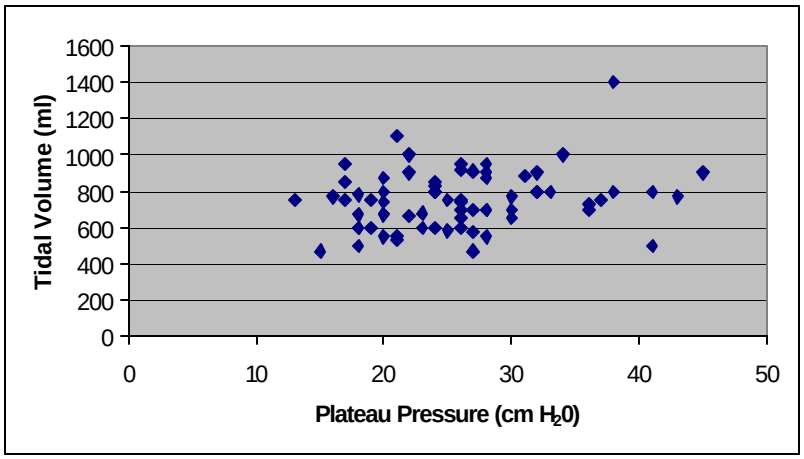

Figure 5: Physician-prescribed tidal volumes (ml/kg PBW) and associated inspiratory airway plateau pressures in ALI/ARDS patients in the survey of New England physicians practices (Appendix B).

7) In the King County survey (Appendix C), there were 131 patients on whom plateau pressures on day 1 were > 30 cm H_2O and who were alive and receiving mechanical ventilation on day 3. Of these 131 patients, the mean change in tidal volume was a reduction of only 30 ml (0.4 ml/kg). These data strongly suggest that physicians were not concerned with plateau pressure, which is considered by many to be the best surrogate indicator for potential overdistention-induced lung injury.

8) Physician-prescribed pre-randomization (baseline) tidal volumes and associated plateau pressures in ARDSNet Study 01 are shown in Figure 3. If physicians had used inspiratory airway pressures to adjust tidal volumes, there would have been an increasing proportion of lower tidal volumes at higher plateau pressures. However, across the wide range of plateau pressures, the frequency distribution of tidal volumes is approximately the same (evenly split above and below 10 ml/kg PBW). This strongly suggests that plateau pressures were not routinely used to adjust tidal volumes.

The main reason that ICU physicians' practices were so variable is that there was no evidence from rigorously conducted studies that physicians could use to prioritize competing clinical objectives. *The purpose of ARDSNet Study 01 was to determine which of the two general approaches to setting tidal volumes and inspiratory pressures would yield better clinical outcomes.* The tidal volume and inspiratory pressure limits used in the two study groups were carefully selected to represent these two approaches while remaining within the scope of ventilatory strategies supported by contemporary opinion and routine clinical practice. More detailed information regarding our choices for targeted tidal volumes and inspiratory pressure limits are provided in our subsequent response to issue A.(5).

ARDSNet Study 01 was not designed to identify the single best approach to mechanical ventilation in ALI/ARDS. However, we reasoned that regardless of the outcome of trial as it was designed, it would provide useful information to improve clinical care or direct future research. We considered, for example, that if the trial showed lower mortality in the lower tidal volume study group, most clinicians would avoid using tidal volumes of 12 ml/kg PBW and higher. Moreover, some clinicians who had tended to favor the traditional gas exchange/breathing comfort approach by using tidal volumes of 9, 10, and 11 ml/kg would consider using lower tidal volumes unless there were compelling reasons not to do so. We considered also that if the trial as designed showed no differences in outcomes, then it would suggest that there was little or nothing to be gained by adjusting tidal volumes or inspiratory pressures within the ranges used in the study. However, we also knew that if ARDSNet Study 01 demonstrated no differences in outcomes between study groups, there would be extensive subset analyses to identify which patients, if any, fared better with one approach or the other. This would be of great value for generating hypotheses to be tested in subsequent studies.

We did not design ARDSNet Study 01 with a routine care group or an average tidal volume group because:

1. *In designing ARDSNet Study 01, we felt that the existence of a U-shaped curve in the relationship of mortality versus plateau pressure (or tidal volume) was very unlikely.* This assessment was based on the following lines of evidence:

    (a) *There had been two case series reports in which mortality in ALI/ARDS patients who received targeted tidal volumes of 5-7 ml/kg measured body weight with inspiratory pressure limits of 30-40 cm H_2O was lower than in historical controls* [3, 4].

    (b) In a preliminary report of a randomized trial [16], the targeted tidal volume in a lower tidal volume study group was $\leq$ 6 ml/kg measured body weight. *The mortality rate in this lower tidal volume group was 33%, which was low relative to historical controls.*

    (c) *A study of patients with acute respiratory failure entitled "Are low tidal volumes safe?" concluded that routine use of low tidal volumes (6 ml/kg) was safe* [22].

(d) A Phase II trial of traditional versus lower tidal volume ventilation was in progress at one of the ARDSNet centers in 1995, when ARDSNet Study 01 was designed. One of the objectives of this phase II study was to assess the safety of a lower tidal volume strategy in ALI/ARDS patients. Targeted tidal volumes (and inspiratory pressure limits) in this phase II study groups were 10-12 ml/kg PBW (45-55 cm H_2O) and $\leq$ 8 ml/kg PBW (30 cm H_2O). *In 1995, an interim analysis by an independent DSMB had reported no safety concerns with either study group.* This trial stopped in March, 1996, immediately before ARDSNet Study 01 started. Data monitored for safety included mortality rates, requirements for gas exchange support (PEEP and FiO_2), fluid balances, requirements for vasopressors, requirements for sedative and neuromuscular blocking medications, barotrauma events, and electrolyte concentrations. The investigators concluded that the lower tidal volume approach used in the study was safe [23]. The mortality rates for both groups in this study were consistent with those in historical controls.

(e) *ARDSNet Study 01 was designed to use a method for setting tidal volumes that was more precise and appropriate for individual patients' lung volumes than the method used in routine care.* According to routine care, tidal volumes are set according to measured body weight. Lung volumes and capacities can be reliably predicted from gender and height [24, 25]. However, measured body weight usually exceeds lean or ideal body weight as calculated from gender and height. (In ARDSNet Study 01, mean measured body weight exceed PBW by 20 %.) Lung volumes and capacities do not change if measured body weight deviates from lean body weight. ARDSNet Study 01 procedures set tidal volumes according to a lean body weight predicted from gender and height. Thus, the study procedures administration of tidal volumes that were excessive relative to the size of individual patients' lungs, which was common in routine care.

(f) *ARDSNet Study 01 procedures were designed to maintain tidal volumes more consistently within safe limits than occurred in routine care*. Tidal volumes and associated airway pressures were monitored closely in a joint effort by on-site study personnel and the clinical teams in the ICUs. The targeted tidal volume in the higher tidal volume group was 12 ml/kg PBW (~10 ml/kg measured body weight), which was very similar to the tidal volumes that were in common use in the 1990s. This is based on personal experiences of the 20 ARDSNet investigators and abundant published literature available to ARDSNet investigators in 1995 (summarized in tables 1, 2 and 3 of the August 19, 2002 letter from Gordon Bernard, M.D. to James Kiley, Ph.D., Director of the Division of Lung Diseases of the NHLBI. See appendix A). The upper limit for acceptable tidal volumes in the higher tidal volume group was 12.5 ml/kg PBW. In ARDSNet Study 01, 97% of tidal volumes in the higher tidal volume group were $\leq$ 12.5 ml/kg PBW. In contrast, the tidal volumes of many patients who received routine care substantially exceeded 12

ml/kg PBW (Figures 1, 2, 3, 4, and 5). In the recent international survey of physicians' practices [20], fully 25% of patients received tidal volumes greater than 12 ml/kg PBW (10 ml/kg measured body weight).

(g) *A growing body of evidence had indicated that protocolized care improves clinical outcomes* [26-31]. Both of our study group protocols included methods for managing several aspects of mechanical ventilation in addition to tidal volumes and inspiratory pressures. These included methods for adjusting FiO_2, PEEP, and I:E ratio to achieve an arterial oxygenation goal; for adjusting respiratory rate, using buffering solutions, and adjusting tidal volumes to achieve a $PaCO_2$/pH goal; and for initiating, monitoring, and progressing with weaning to achieve a spontaneous breathing goal expeditiously. These methods were developed by expert consensus of the ARDSNet investigators, with additional guidance from our protocol review committee and DSMB. Study personnel (ARDSNet investigators, study nurse coordinators, respiratory therapists) provided substantial support to the clinical ICU staffs to assist with implementation of these methods. The surprisingly low number of ventilator days in both study groups (relative to historical controls)suggests that there were substantial beneficial effects of these recommended approaches and the support of the clinical trial personnel.

(h) *ARDSNet Study 01 eligibility criteria specifically excluded patients in whom there was concern that hypercapnia and acidosis could have adverse effects.* These included patients with known or suspected intracranial hypertension, sickle hemoglobin, and those taking tricyclic antidepressant medications.

(i) ARDSNet Study 01 protocol rules were written to minimize hypercapnia and respiratory acidosis, which was anticipated in the lower tidal volume group. These protocol rules reflected contemporary opinions and routine care practices. When there was controversy, the rules allowed judgments according to patients' clinical team:

i. When tidal volumes were reduced, respiratory rates were increased to maintain minute ventilation.
ii. If arterial pH was < 7.30, ventilator set rate was increased (to a maximum of 35 breaths/minute).
iii. If arterial pH was < 7.30, ICU clinicians had the *option* of administering sodium bicarbonate to buffer the pH. The decision to use sodium bicarbonate was left to the judgment of the ICU clinicians.
iv. If arterial pH was < 7.15, ICU clinicians had the *option* to increase tidal volume to achieve higher levels of ventilation (lower $PaCO_2$/higher pH). If this option was used, the protocol inspiratory pressure limit was suspended (acknowledging that in the clinical judgments of the ICU physicians, it was more important to control $PaCO_2$/pH than to maintain low inspiratory plateau pressures).

v. For severe dyspnea, which occurred in some patients receiving lower tidal volumes, clinicians had the *option* of raising tidal volumes to 7 or 8 ml/kg PBW.

(j) *ARDSNet Study 01 procedures required consent from attending physicians before enrollment of their patients.* Attending physicians declined to allow their patients to participate if they had concerns regarding the safety of their patients.

(k) *The ICU staffs were empowered to deviate from any protocol rules if necessary for patient safety.* During the course of the trial, tidal volumes were "off-target" in ~15% and ~22 % of patient days in the traditional and lower tidal volume study groups, respectively. Inspiratory plateau pressures were off-target in ~2% and ~13% of patient days in the traditional and lower tidal volume study groups, respectively.

(l) *The trial design required frequent interim analyses by an independent safety monitoring committee (DSMB).* These analyses occurred after completion of study procedures by groups of approximately 200 patients. Study personnel were required to report all adverse events that could be attributed to the study procedures. At each interim analysis, the DSMB received detailed unblinded reports that included adverse event experiences, physiologic data, and clinical outcomes in the two study groups. The trial would have been halted at any of these interim analyses if there were significant concerns regarding safety of either study group.

Thus, there were several lines of evidence against a U-shaped relationship of mortality versus tidal volume/plateau pressure, and numerous safeguards and trial design safety procedures protected patients in both study groups against risks that frequently occur in routine practices. Therefore, *it was very unlikely that mortality in a routine care study group would be lower than either the 6 ml/kg and 12 ml/kg protocol groups.* (Additional, more direct evidence against the U-shaped relationship became available after completion of ARDSNet Study 01 to validate this belief. This evidence is reviewed in our subsequent response to issue A.(7).) Therefore, we believed that *a trial design that included only 2 study groups (6 ml/kg and 12 ml/kg) would be as safe or safer than a trial design that included a routine care group in a third arm.*

2. As shown in our previous responses to issue A.(1)(b), routine care for tidal volumes and inspiratory pressures can be defined only by broad ranges. Within these broad ranges, there were no clearly understood principles for adjusting ventilator parameters because there was very little evidence from rigorously conducted clinical studies that physicians could use for prioritizing competing clinical objectives. Had we included routine care as a control group, some tidal volumes and inspiratory pressures would have been set according to intensivists' highly variable estimations of risks and benefits of the two general approaches for prioritizing competing clinical objectives.

Some tidal volumes and inspiratory pressures would have been set by attending physicians who were not specially trained and experienced in critical care. Some tidal volumes would have been set by residents or respiratory therapists who were supervised by intensivists who did not believe the settings could make any difference as long as they were within the broad limits of routine care. These practices are highly variable from one another at any one point in time, and they may shift over the 3 year course of a clinical trial such as ARDSNet Study 01. As explained in our subsequent response to issue A(1)(c), it would be very difficult or impossible to enlighten clinical practice by comparing mortality in a routine care control group, in which practices are so variable and difficult to define, to mortality in a protocolized study group.

3. *Inclusion of a third arm in the trial would have increased the costs to society for conducting the study and could have prevented its successful completion.* As designed with two arms (12 ml/kg and 6 ml/kg), the maximum enrollment of ARDSNet Study 01 was 1000 patients. We estimated that we would complete the trial in 3 years. If we had designed the trial with 3 arms (12 ml/kg, 6 ml/kg, and routine care), the sample size required to complete the study would have been substantially greater. A three-arm trial would have required at least 1500 patients for completion. This is the number that would have been required if we assumed that mortality in the routine care and 12 ml/kg groups were both 50% and that mortality in the 6 ml/kg arm was 40%; and if we made no statistical adjustment for multiple comparisons. If we had estimated that mortality in the routine care group was intermediate between the 6 ml/kg and 12 ml/kg groups (e.g. 45%), and if the trial was designed to prove that the 6 ml/kg study group was better than routine care, then the study would have required approximately 4000 patients for completion. This 3-arm study would have required approximately 12 years to complete. Because clinical substrates and clinical practices change over time, the relevance of such a trial results to clinical practices at the time of completion of the trial (if completion were possible) would be greatly diminished. The resources committed to the trials would not be well-utilized. Moreover, risks to study participants (if any) may not be justifiable in relation to the value of the information gained.

We did not include a control arm that allowed tidal volumes anywhere in the range of 7-11 ml/kg PBW. This is a relatively broad range of tidal volumes which, when applied to a population of ALI/ARDS patients in whom lung compliance varies widely, would result in a very broad range of inspiratory airway pressures. Thus, this would result in a study group that resembled routine care. As explained in the preceding paragraphs. For reasons given in our previous (and subsequent) responses, we believed there would be little value to including such a control group in ARDSNet Study 01. On the other hand, including such a control group would have increased the costs to society for conducting the trial and could have prevented its successful completion.

(c) Because of the apparent failures noted in (a) and (b) above, the study appears to have lacked a control group appropriate for such a phase III clinical trial. Specifically, the study appears to have lacked a control group that received either of the following:

> ***(i) Individualized mechanical ventilation management with tidal volumes and plateau airway pressures set at levels anywhere along the spectrum of these variables based upon consideration of a number of complex clinical factors unique to each subject, and the expertise, training and clinical judgment of a team of intensive care physicians (hereafter referred to as a "standard of care" tidal volume control group); or***
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> [As explained in the cover letter that accompanies this response, OHRP has used the terms "routine care" and "standard of care" interchangeably. ARDS Network investigators prefer to use the term "routine care" instead of "standard of care".]

The preceding statement by OHRP implies that there were clearly understood principles for adjusting tidal volumes and inspiratory pressures, and that physicians adhered to these principles. As shown in our responses to issues A.(1)(b), routine care for tidal volumes and inspiratory pressures can be defined only by broad ranges. Within these broad ranges, there were no clearly understood principles for adjusting ventilator parameters because there was very little evidence from rigorously conducted clinical studies that physicians could use for prioritizing competing clinical objectives. Had we included routine care as a control group, some tidal volumes and inspiratory pressures would have been set according to intensivists' highly variable estimations of risks and benefits of the two general approaches for prioritizing competing clinical objectives. Some tidal volumes and inspiratory pressures would have been set by attending physicians who were not specially trained and experienced in critical care. Some tidal volumes would have been set by residents or respiratory therapists who were supervised by intensivists who did not believe the settings could make any difference as long as they were within the broad limits of routine care. These practices are highly variable from one another at any one point in time, and they may shift over the 2-3 year course of a clinical trial such as ARDSNet Study 01. In the following paragraphs, we consider the potential value *and the risks to participants* of including a routine care group in two alternative trial designs.

<u>Alternative trial design #1</u>: We could have used a routine care group (or a tidal volume = 7-11 ml/kg PBW) *instead of* the traditional tidal volume group, in which the targeted tidal volume of 12 ml/kg PBW was closer to the mean, median, or mode tidal volumes used in routine care. We did not adopt this trial design because the control group would have included such heterogeneous practices, as shown in responses to issues A.(1)(b), that individual physicians would not know if the results of the trial were applicable to their own practices. For example, consider a trial in which mortality in the routine care group was 5% higher than in the study group that received a targeted tidal volume of 6 ml/kg (with plateau pressure limit of 30 cm H_2O). Most physicians would attribute this mortality difference to the patients who were managed in the routine care group with the tidal volumes and inspiratory pressures that were considerably higher than average. They could deny the possibility that their own practices within routine care were problematic. Thus, the knowledge gained from such a trial would be of little value, and the resources expended and risks to study participants (if any) would not be justified. We would have failed in our commitments to our study participants, many of whom agree to participate in research studies because they want to contribute to medical progress. This unsound study design would have been in violation of CFR 46.111(a), which requires that risks to subjects are

reasonable in relation to the importance of the knowledge that may be reasonably expected to result.

Alternative trial design #2: We could have included a routine care (or a tidal volume = 7-11 ml/kg PBW) group as a third study group in a trial that included both the 12 ml/kg and 6 ml/kg PBW targeted tidal volume protocols. We did not adopt this trial design because, as explained in the preceding paragraph, the comparisons of outcomes between a routine care study group and each of the other two study groups would not enlighten clinical practice. Therefore, the only value of including a routine care study group in this trial design would be to provide assurance that the two protocolized study groups were not harmful relative to routine care. However, we had ample reason to believe that our two study group protocols were safe relative to the routine care (reasons given in previous response to issue A.(1)(b)). On the other hand, inclusion of a third arm in the study would have increased costs to society for gaining the same information and could have prevented successful completion of the trial.

To summarize regarding the alternative trial designs that include a routine care group (or a tidal volume = 7-11 ml/kg group):

1. Comparisons of outcomes between a routine care control group (or a tidal volume = 7-11 ml/kg control group) would have provided little useful information to guide clinical practice because practices within a routine care (or a tidal volume = 7-11 ml/kg group) would have been so variable that the results of the study would have been of little value for changing clinical practice..
2. Inclusion of a routine care study group (or a tidal volume = 7-11 ml/kg group) in a three-arm study could provide some assurance that the two protocolized study groups were not harmful relative to routine care. However, there was, a priori, ample reason to believe that the two protocolized study groups were safe relative to routine care.
3. Inclusion of a routine care study group (or a tidal volume = 7-11 ml/kg group) in a three-arm study would have substantially increased the cost to society for gaining the same information that was obtained with the two-arm trial that was conducted in ARDSNet Study 01.

The study design used in ARDSNet Study 01 (i.e., two study groups with explicit protocol rules to control the key variables under study) has been used in many previous and ongoing clinical trials. For example, a recent trial compared clinical outcomes in critically ill patients randomized to receive blood transfusions according to two different explicit protocols that represented different schemes for prioritizing competing clinical objectives [32]. Before this study, physicians' standard care transfusion practices were highly variable. As with tidal volumes and inspiratory pressures in ALI/ARDS patients, routine care for deciding when blood should be transfused included a broad range of acceptable hematocrit or hemoglobin thresholds. Within these broad ranges, there were no clearly understood principles to which physicians adhered because there was no evidence from rigorously conducted clinical studies to guide physicians who must choose between competing clinical objectives. Neither of the study protocols attempted to simulate standard care because, in fact, the principles for conducting standard care were not defined. The result of this trial, which demonstrated better outcomes with

a lower hemoglobin transfusion threshold, has provided valuable evidence to guide clinical practice. Another recent trial compared clinical outcomes in patients with pulmonary embolism randomized to receive anticoagulant/thrombolytic therapy according to two different explicit protocols that represented different schemes for prioritizing competing clinical objectives [33]. In countless phase III trials of chemotherapeutic strategies, study groups received therapy according to explicit study protocols that represented either an accepted approach or a new approach to management. Even when study groups were considered "control groups", the study protocols did not allow standard care practices. Without controlling the key aspects of treatment, there would be countless variations in physicians' choices of medications, dose, and timing according to physicians' practice styles, preferences, abilities, and external influences. It would be impossible to characterize the study groups, and the results of the studies would be of very little value for guiding clinical practice. There has been substantial progress in clinical trial design in the past 50 years. One of these advances is the recognition that clinical practices are highly variable for reasons that are unrelated to sound evidence. One cause of these practice variations is that physicians are sometimes torn between competing intermediate objectives which are of unclear significance in relation to the most important clinical outcomes. At other times the practice variations are due to differences in physicians' irrational biases and practice styles. By controlling the key aspects of therapy in both study groups while remaining within the scope of routine clinical care, the ARDS Network trials (and many other clinical trials) provided high quality evidence to advance medical care and direct future clinical research. None of these studies were designed to determine a single best approach for all patients, and none were conducted simply to answer a physiologic question. All of these studies examined components of practice, such as tidal volume or transfusion threshold, in which there was substantial practice variation because of uncertainty about the clinical importance of different intermediate objectives. Each of these studies provided essential building blocks for sound evidence-based practices.

(ii) protocol-mandated mechanical ventilation management with a tidal volume set at a level representing, as appropriate based upon systematic assessment of routine clinical practice, the mean, median, mid-range or mode of tidal volume levels used in routine clinical practice at the time the study was conducted (hereafter referred to as an "average" tidal volume control group). For the ARMA study, this presumably would have been a tidal volume set somewhere between 7 and 11 ml/kg PBW.

OHRP suggests that ARDSNet Study 01 should have included a control group with "protocol-mandated mechanical ventilation management with a tidal volume set at a level representing … the mean, median, mid-range or mode of tidal volume levels used in routine clinical practice … (…'average' tidal volume control group)." There are several reasons why we did not include such a control group.

a. In ARDSNet Study 01, the mean, median, and mode of the pre-randomization tidal volumes were all within the range of 10-11 ml/kg PBW. However, this narrow range of baseline tidal volumes includes

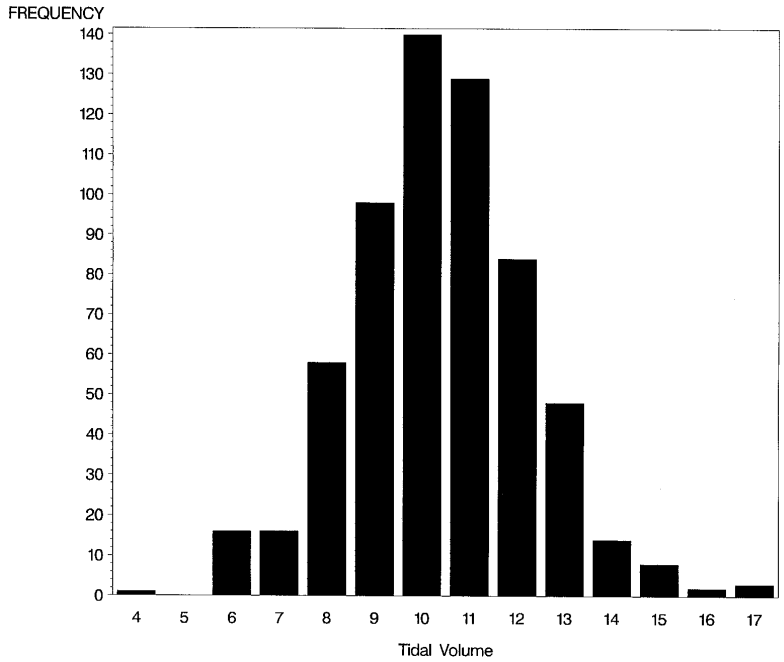

Figure 6: Frequency distribution of tidal volumes that physicians had prescribed for ALI/ARDS patients before enrollment in ARDSNet Study 01. Tidal volumes are shown in ml/kg predicted body weight.

only 24% of all patients in the ARDSNet Study 01. For comparison, 13% of the pre-randomization tidal volumes in ARDSNet Study 01 were in the range of 8-9 ml/kg PBW, and 20% were in the range of 9-10 ml/kg PBW. The pre-randomization tidal volume range of 11.5-12.5 ml/kg PBW (which encompasses most of the tidal volumes used in the 12 ml/kg PBW study group) included 15% of all patients on whom pre-randomization tidal volumes were available. Therefore, the 12 ml/kg PBW tidal volume protocol range represented a proportion of pre-randomization tidal volumes that was similar to the proportions represented by other similarly narrowly defined ranges and therefore represented a reasonable choice for one of the arms of our trial. The averages of the tidal volumes that were used by physicians simply represent the averages of physicians' greatly disparate practices, not routine care Therefore, an average tidal volume group would not be an accurate representation of routine care.

b. Inclusion of an average tidal volume study group in a three-arm trial (with the 6 ml/kg and 12 ml/kg PBW groups) could be useful *only* to indicate if the 6 ml/kg and 12 ml/kg study protocols were superior or inferior to the average tidal volume protocol. However, inclusion of an average tidal volume study group would not rule-out the possibility of a nadir in mortality at some tidal volume between 6 and 12 ml/kg PBW unless the tidal volume associated with the nadir was close to the average tidal volume. Consider for example a theoretical scenario in which mortality rates at 12 ml/kg PBW, 8 ml/kg PBW, and 6 ml/kg PBW (with the associated inspiratory airway pressures) are 40%, 25%, and 30%, respectively. If we designed ARDSNet Study 01 with a third study group with targeted tidal volume = 10 ml/kg PBW (the mean tidal volume used by clinicians before

patients were randomized in the study), the resulting mortality rates would have been approximately 40%, 33%, and 30%. This trial would not have demonstrated the nadir in the relationship of mortality versus tidal volume/inspiratory pressure between 12 ml/kg and 6 ml/kg PBW. The added information would not have contributed substantially to the knowledge gained from ARDSNet Study 01 as it was designed and conducted. However, inclusion of the third arm in trial would have increased the costs to society for gaining the same information as a trial with two arms and could have prevented its successful completion.

To determine if there is a nadir in the relationship of mortality versus tidal volume (or inspiratory airway pressure), a study would require randomization of patients to many different study groups, each with a different targeted tidal volume and inspiratory pressure limit. Such a trial would not be feasible. We believed the possibility of this nadir in the range of 6-12 ml/kg PBW was remote. Moreover, because such a study would have required enrollment of thousands more patients, it would have increased risk to more patients (relative to 6 ml/kg or 12 ml/kg PBW, whichever was better) than a simpler trial with only two study groups. Therefore, the most sensible trial design in relation to patient safety as well as feasibility was a two-arm trial, as we conducted in ARDSNet Study 01.

c. If we had used an average tidal volume study group instead of the protocolized 12 ml/kg PBW study group, it would have increased risk to more patients. With an average tidal volume study group instead of the 12 ml/kg PBW study group, the difference between the study group target tidal volumes would have been reduced, and the between-group difference in mortality would also be reduced. Assume that mortality for study groups with targeted tidal volumes of 12 and 6 ml/kg are 50% and 40%, respectively (the same mortality rates assumed for the sample size calculation for ARDSNet Study 01). If the average tidal volume was 10 ml/kg PBW, then by interpolation between the assumed mortalities in 6 and 12 ml/kg groups, the mortality in the average tidal volume study group would be 47%. Assume also that the trial is designed with type I and type II errors of 0.05 and 0.11, respectively, as in the trial design of ARDSNet Study 01.

<u>Comparison of risks to study participants</u>:

Trial of 6 ml/kg vs. 10 ml/kg PBW
Sample size required = 1015 per study group.

In this trial, there would be 477 deaths (.47 x 1015) in the 10 ml/kg group and 406 deaths (.40 x 1015) in 6 ml/kg group. The number of excess deaths (relative to the number of deaths that would have occurred if all patients received the better of the two treatments) would be 71.

Trial of 6 ml/kg vs. 12 ml/kg PBW
Sample size required = 500 per study group.

In this trial, there would be 250 deaths (.50 x 500) in the12 ml/kg group and 200 deaths (.40 x 500) in 6 ml/kg group. The number of excess

deaths (relative to the number of deaths that would have occurred if all patients received the better of the two treatments) would be 50.

Thus, the number of excess deaths is greater in the trial in which the control group target tidal volume was the average (10 ml/kg PBW) rather than 12 ml/kg PBW. *The numbers of deaths in the study groups would be different if early stopping rules caused the trials to stop early. However, the effects of early stopping rules are extremely difficult to predict, so the calculations are based on the assumption that the trials continue to the maximum planned enrollment.*

(d) As a result of (a)-(c) above, there appears to be insufficient evidence to support any conclusions that mechanical ventilation management with low tidal volume intervention (6ml/kg) is superior to either of the following:

ARDSNet Study 01 was not designed to demonstrate the superiority of 6 ml/kg versus routine care or average tidal volume care. Instead, ARDSNet Study 01 was designed to determine if clinical outcomes would be better with a mechanical ventilation strategy that gave higher priority to lung protection than a strategy that gave higher priority to maintaining gas exchange and breathing comfort. This study provided useful information to intensivists who need guidance in their clinical practices and contributes to an emerging foundation on which a routine care can become "best care".

(i)Individualized "standard of care" mechanical ventilation management; or

As explained in our previous response to issue A.(1)(b), routine care for mechanical ventilation management in the 1990s, when ARDSNet Study 01 was designed and conducted, was defined by broad ranges of tidal volumes and inspiratory pressures. Within this routine care, clinicians could use either a traditional or a lung-protective approach or any of a number of approaches that represented varying degrees of hybridization of the traditional and lung-protective approaches. Therefore, we have made no conclusions regarding the superiority of low tidal volume ventilation versus routine care. It is likely that the 6 ml/kg protocol yielded better outcomes than the approaches which, within routine care, tended to favor the traditional gas exchange/breathing comfort approach. It is likely also that the 6 ml/kg protocol yielded outcomes that were similar to those that resulted from the approaches that, within routine care, favored lung-protection. The data presented later in response to issues A.(7) indicate that overall mortality was probably lower among patients randomized to the lower tidal volume study group than those managed by routine care.

(ii) mechanical ventilation management with tidal volumes routinely set at a level between 7 and 11 ml/kg PBW.

ARDSNet Study 01 was not designed to prove the superiority of 6 ml/kg versus tidal volumes routinely set at a level between 7 and 11 ml/kg PBW. The tidal volume range of 7-11 ml/kg PBW is relatively broad. Within this range, clinicians could use either a traditional or a lung-protective approach or any of a number of approaches that represent varying degrees of hybridization of the traditional and lung-protective approaches. It is likely that the 6 ml/kg protocol yielded better outcomes than the approaches that, in routine care, tended to favor the traditional gas exchange/breathing comfort approach. On the other hand, it is likely also that the 6 ml/kg protocol yielded outcomes that were closer to those that resulted from the approaches that, in routine care, favored lung-protection. We can make no definitive conclusions regarding the superiority of low tidal volume ventilation versus an approach that used tidal volumes at a

level between 7 and 11 ml/kg PBW. However, the data and analyses provided in our subsequent responses to issues A.(7) strongly suggest that reducing tidal volumes to achieve lower plateau pressures results in lower mortality, even when plateau pressures before tidal volume reduction are in a range that some have thought were safe (e.g. plateau pressures below 30 cm H_2O). This analysis strongly suggests that a targeted tidal volume of 6 ml/kg PBW will result in lower mortality than targeted tidal volumes between 7 and 11 ml/kg PBW.

(e) As a result of (a)-(c) above, both groups of experimental subjects in the ARMA study may have been placed at an increased risk of death in comparison to patients managed according to a "standard of care" tidal volume control group strategy or an "average" tidal volume control group strategy because:

(i) The two experimental groups received mechanical ventilation with tidal volumes set at levels that may have been lower or higher than the levels of tidal volumes most commonly used in routine clinical practice; and

We agree that some patients enrolled in ARDSNet Study 01 received tidal volumes that were higher or lower than those they would have received in routine clinical care. Justification for this approach is given in our previous response to issue A.(1)(b). For reasons given in our response to issue A.(1)(b), we did not believe that participants in either study group in ARDSNet Study 01 would be subjected to increased risks relative to routine care.

(ii) the relationship of mortality to tidal volume may be quadratic, resulting in a U- or J- shaped curve (the existence of a U-shaped curve was acknowledged by the ARDSNet investigators at the August 30, 2002 meeting convened by NHLBI).

Also for the high (traditional) tidal volume group, exposure to significantly higher plateau pressures (as high as 50 cm H_2O per the ARDSNet protocol) may have contributed further to an increased risk of death.

On August 30, 2002 we acknowledged the *theoretical possibility* of a U- or J-shaped relationship of mortality versus tidal volume or plateau pressure. This acknowledgment was in response to a question from OHRP that opened the realm of possible tidal volumes and plateau pressures to extreme limits. In 1995, when ARDSNet Study 01 was designed, there was no evidence for a U- or J-shaped relationship over the ranges of tidal volumes and inspiratory airway pressures that we planned to use. However, since completion of ARDSNet Study 01, analyses of the study database strongly suggest that the relationship is not U- or J-shaped over the relevant ranges of volume and pressure. The first line of evidence is shown in Figure 7 in our subsequent response to issue A.(7). This graph of mortality versus plateau pressure and the logistic regression also described in our response to issue A.(7) strongly suggest that the beneficial effect of decreasing plateau pressure continues to the lowest plateau pressures experienced in the ALI/ARDS patients enrolled in ARDSNet Study 01. Also included in our response to issue A.(7) is a table of mortality rates and plateau pressures in quartiles of patients defined by plateau pressures in the two study groups. This table shows that among patients whose plateau pressures were < 32 cm H_2O while receiving tidal volumes of 12 ml/kg PBW, mortality would have been lower had they received 6 ml/kg PBW (with associated lower plateau pressures). The data in Figure 7 and the following table in our response to issue A.(7) indicate that plateau pressures < 32 cm H_2O should not be considered "safe". *These analyses are inconsistent with a U- or J-shaped relationship of mortality versus tidal volume in the range of tidal volumes and plateau pressures used in ARDSNet Study 01.*

With hindsight (after completion of ARDSNet Study 01), some will suggest that mortality in the 12 ml/kg PBW study group was higher than it would have been if the patients had not participated in the study. However, this is very unlikely for the following reasons: 1) The targeted tidal volume in this study group was 12 ml/kg PBW, and the upper limit for acceptable tidal volume in this group was 12.5 ml/kg. This upper limit was rarely exceeded in study patients. In contrast, the upper limit for tidal volumes or inspiratory pressures in patients who were not enrolled in this study was considerably higher, as explained in our previous responses to issue A.(1) and as shown in Figures 1, 2, 3, 4, and 5. 2) The 12 ml/kg protocol included expert consensus approaches for adjusting PEEP, FiO_2, and I:E ratio to support arterial oxygenation; for adjusting respiratory rate and tidal volume to manage acid-base balance; and for weaning. A substantial body of evidence demonstrates better clinical outcomes when protocols such as these are applied to routine clinical practice [26-31].

(f) As a result of (a)-(c) above, any increased risk of death for the two experimental groups of study subjects may have gone undetected because of the failure of the ARMA study design to include either a "standard of care" tidal volume control group or an "average" tidal volume control group.

As explained in our response to issue A.(1)(b), published studies [3, 4, 16, 22] and an ongoing phase II study [23] had supported both of our study protocols as safe relative to routine care. Moreover, as explained in A.(1)(b), numerous safeguards were built into the study protocols of ARDSNet Study 01. Therefore, in 1995, we did not believe that either of our study groups was subjected to increased risks relative to routine care. As explained in our response to issue A.(1)(e), additional analyses after completion of ARDSNet Study 01 indicate that *even if a routine care study group had the same safeguards as those built into our study group protocols, mortality in the lower tidal volume study group would have been lower than in a routine care study group*. The mortality rate of 40% in the group that received higher tidal volumes in ARDSNet Study 01 was very similar to (or lower than) the mortality rates reported in similar studies of similar patients conducted in the 1990s [17, 23, 34, 35]. For example, overall mortality was 40% in a large, multicenter study in ARDS patients *in which all ventilator settings were controlled by physicians caring for the study participants* [17]. Also, the mortality rate of 31% in the study group that received lower tidal volumes in ARDSNet Study 01 is *lower than the mortality rate reported for any other large group of patients in a multicenter study.*

As explained in our response to issue A.(1)(c), an average tidal volume group would have represented only ~24% of the practices of all physicians whose patients were enrolled in ARDSNet Study 01. This proportion does not fairly represent the routine care, and it is only slightly more than was represented by our 12 ml/kg PBW study group. Inclusion of such a study group would have been of very little value, but it would have increased the cost to society for conducting the trial and could have prevented its successful completion.

Inclusion of a routine care or average care group in clinical trials of care processes (such as tidal volumes and transfusion thresholds) has not been adopted as a necessary design to assure patient safety. Instead, careful design strategies and oversight, as conducted in ARDSNet Study 01, represents the standard for trial design.

(g) In response to these previously presented concerns, the ARDSNet investigators have stated that there is no standard of care for patients with ALI and ARDS on mechanical ventilation with respect to tidal volume settings and plateau airway pressures and the levels of tidal volumes selected for the two experimental groups were within the range used in routine clinical practice.

OHRP acknowledges that the two tidal volumes were within the range used in routine clinical practice at the time when the study was designed and conducted. However, "within the range used in routine clinical practice" and "routine clinical practice" are not equivalent concepts. Presumably, in routine clinical practice, at the time the study was initiated, patients with ALI and ARDS were treated with mechanical ventilation using tidal volumes selected from anywhere along the continuum for tidal volume based upon the expertise, training and clinical judgment of a team of intensive care unit physicians, taking into consideration a number of complex clinical factors unique to each subject. Presumably, such routine clinical practice did not result in patients being placed on either 6 ml/kg or 12 ml/kg PBW based upon random choice.

Please respond in detail to each of the above items.

As illustrated in the data included in our responses to issues A.(1)(a) and (b), routine care for tidal volumes and plateau pressures could only be defined by broad ranges of acceptable tidal volumes and plateau pressures.

We agree that "within the range used in routine clinical practice" and "routine clinical practice" are not equivalent concepts. However, we do not agree with how OHRP interprets the broad ranges of tidal volumes and associated inspiratory airway pressures that occur in routine clinical practice. OHRP suggests that as part of routine clinical practice, tidal volumes are "selected from anywhere along the continuum for tidal volume based upon the expertise, training, and clinical judgment of a team of intensive care unit physicians, taking into consideration a number of complex clinical factors unique to each subject." This assumes that there were clearly understood principles for setting and adjusting tidal volumes and inspiratory pressures within the broad ranges of routine or standard care; and that physicians adhered to these principles. As explained in our previous response to issue A.(1)(b), the primary reason for the broad ranges of tidal volumes and inspiratory pressures in routine care practices is that there were no clearly understood principles that physicians understood or to which they adhered. There is very little if any evidence that after prescribing initial ventilator settings, clinicians adjusted tidal volumes or inspiratory pressures in relation to physiologic characteristics of individual patients.

We agree that if patients not enrolled in ARDSNet Study 01 received 6 ml/kg or 12 ml/kg PBW, it may not have been based upon random choice by their physicians. If a patient received 6 ml/kg (or 12 ml/kg), it could have been because his/her physician believed that the lung-protective lower tidal volume prioritization scheme (or the gas exchange/breathing comfort traditional tidal volume scheme) was preferable. Importantly, if patients received *any* tidal volume along the continuum (including 7, 8, 9, 10, and 11 ml/kg), their physicians were making *equivalent best-guess estimations of risks and benefits.* Without good evidence from rigorously conducted clinical studies, *there was no more good clinical judgment or expertise behind the choice of any tidal volume in the range of 5-15 ml/kg (or inspiratory pressure limit) than with any of the other options*. Now that ARDSNet Study 01 is complete, physicians can make clinical

decisions with more clinically relevant evidence. More patients will receive lower tidal volumes now than in the past, and more will survive.

(2) Please clarify whether or not, prior to designing the ARMA study, the ARDSNet investigators conducted a pre-study review and analysis of routine clinical practice within the intensive care units of participating ARDSNet institutions in order to determine the range and frequency distributions of tidal volumes and plateau airway pressures used in actual clinical practice to treat the type of patient population that would have been eligible for the ARMA clinical trial. In your response, please address the following, as appropriate:

(a) If such a pre-study review and analysis was conducted, please provide the complete results of that review and analysis.

As explained in our response to issue A.(1)(a), we did not conduct a pre-study review and analysis of the range and frequency distribution of tidal volumes and plateau pressures used in routine clinical practice in the ICUs of the ARDSNet hospitals. The previously cited survey of intensive care physicians' mechanical ventilation practices [1] was available to us in 1995, when we designed ARDSNet Study 01. This survey demonstrated a broad range of initial tidal volumes that intensivists reported using in ARDS patients. ARDS Network investigators also reviewed many previous studies that reported tidal volumes used by practicing physicians. ARDS Network investigators contributed to many of these studies. These studies, which showed broad ranges of physician-selected tidal volumes, were previously summarized in Tables 1,2, and 3 of the letter of August 19, 2002 from Gordon Bernard, MD to James Kiley, Ph.D., Director of the Division of Lung Diseases of the NHLBI. (See Appendix A.) These data were consistent with ARDSNet investigators' knowledge of their own and their colleagues' practices at their home institutions. From these data, experiences, and conflicting authoritative recommendations [2, 4, 5, 7], it was apparent that there were two different approaches for prioritizing competing clinical objectives. It was also apparent that physicians working in the ARDS Network intensive care units sometimes favored one approach over the other and sometimes used approaches that represented varying degrees of hybridization of the two approaches.

ARDSNet Study 01 procedures were reviewed by an independent protocol review committee and an independent data and safety monitoring board. Both of these committees included experts on mechanical ventilation who used their knowledge of current practices, the literature, and their own experiences to assess the safety of the trial design. The institutional review boards of the ARDS Network hospitals also reviewed ARDSNet Study 01 procedures for safety and appropriateness of trial design. All of these committees considered ARDSNet Study 01 to be appropriately designed, safe, and ethical.

(b) If no such review and analysis was conducted, please clarify whether such a review and analysis was considered and explain the reasons for deciding not to perform such a review and analysis.

We did not consider conducting another review of the range and frequency distribution of tidal volumes and inspiratory pressures used in actual clinical practice. As explained in our previous responses to issues A.(1) and A.(2)(a), there was abundant evidence from published studies, authoritative reviews, and personal experiences. These sources indicated that routine care for tidal volumes and inspiratory pressures was defined by broad ranges. The data presented in response to issue A(1)(b) indicates that within these broad ranges, physicians did

not recognize or adhere to any standard for adjusting tidal volumes in relation to airway pressures or any other patient-specific factor.

(c) Please clarify whether the investigators or IRB at any participating institution requested such a pre-study review and analysis prior to approving the research. If so, please provide all correspondence and pertinent IRB records related to such a request.

For the reasons stated above in responses to issues A.(1) and A.(2), further pre-study reviews were not necessary. None of the IRBs at any participating institutions requested such a pre-study review and analysis prior to approving the research. We can recall no such request by any of the investigators.

(3) If no such data are available with respect to the type of pre-study review and analysis described in item (2) above, please arrange for each site that participated in the ARMA trial to conduct a review of the clinical records for a representative consecutive sample of patients who were diagnoses with ALI or ARDS and would have satisfied the study enrollment criteria immediately prior to the initiation of enrollment of subjects at the site. Based upon this review, please provide the following:

(a) Number of patients reviewed for each site.

Will require site chart review.

(b) Date on which ventilator therapy was initiated for each patient.

Will require site chart review.

(c) A frequency distribution of the tidal volume used and plateau airway pressures measured on days 1, 3, and 7 of ventilator therapy for each ARDSNet study site and for all sites combined.

Most of the ARDS Network centers did not keep logs of ALI/ARDS patients before initiating ARDSNet Study 01. Keeping such a log is labor intensive, and there was no support for such efforts before our studies were initiated. Therefore, it is not possible to provide the requested data on consecutive samples of patients with ALI or ARDS at all of the ARDS Network hospitals.

(4) Please clarify whether the ARDSNet investigators would consider the levels of tidal volume used and plateau airway pressures measured in subjects prior to randomization in the ARMA study to be useful for defining the range and frequency of tidal volumes used and plateau airway pressures measured in routine clinical practice outside the research context at the participating ARDSNet study sites. If not, please explain why.

The tidal volumes used and the associated plateau pressures measured in subjects prior to randomization in ARDSNet Study 01 are probably close to those that would be measured in routine clinical practice outside the research context at the participating ARDSNet study sites. However, we believe these pre-randomization tidal volumes were probably lower than those that would have been measured in routine clinical practice. The reason for this difference is that our conduct of ARDSNet Study 01 raised awareness of the concerns regarding excessive pressure, volume, and stretch on the part of clinicians practicing in our ICUs. We believe this heightened awareness caused some practicing clinicians to shift their practices during the course of ARDSNet Study 01 towards use of smaller tidal volumes.

The physician-prescribed tidal volumes recorded before randomization in ARDSNet Study 01 are similar to or slightly lower, on average, than the tidal volumes reported in surveys and

studies reported up to 1995. The main value of these surveys in the context of this discussion was to define the broad limits of routine practice. We used the data from surveys such as these to determine the targeted tidal volumes of 6 and 12 ml/kg PBW in ARDSNet Study 01. These tidal volumes were consistent with contemporary opinions and within the scope of routine clinical practice.

(5) Please explain the basis for selecting the two experimental groups (6 ml/kg and 12 ml/kg PBW). Was there any basis pre-study to assume that these two tidal volumes would be safer and more effective than tidal volumes ranging from 7 to 11 ml/kg PBW? Were the tidal volumes for the two experimental groups selected based upon the expectation that this would increase the likelihood of showing a statistically significant difference between the two experimental groups?

Rationale for the 12 ml/kg protocol

We selected the target tidal volume of 12 ml/kg PBW to be consistent with the range of 10-15 ml/kg, which is the range of tidal volumes recommended for years in an approach that gave high priority to maintaining gas exchange and breathing comfort [2, 5-7]. Importantly, we set tidal volumes in ARDSNet Study 01 according to a body weight that was predicted from gender and height (predicted body weight, PBW) because these parameters are good predictors of measured lung volumes [24, 25]. Deviations of measured body weight have trivial effects on measured lung volumes [36]. In ARDSNet Study 01, the mean measured body weight exceeded mean PBW by 20%. Therefore, 12 ml/kg PBW was equivalent to approximately 10 ml/kg measured body weight, which was near the lower end of the traditional range of tidal volumes recommended for the approach that prioritized gas exchange and breathing comfort. In this context, it is notable that the mean tidal volume that physicians prescribed in their practices in the early-mid 1990s was also close 10 ml/kg MBW (equivalent to 12 ml/kg PBW). In the Exosurf study [17], the mean tidal volume prescribed by clinicians was 11.4 ml/kg MBW. In the ibuprofen in sepsis study [19], in which most patients had acute lung injury, the mean physician-prescribed tidal volume was 10.3 ml/kg measured body weight.

There is virtually no published information regarding plateau pressure limits that physicians used to adjust tidal volumes. In the previously cited survey of intensive care physicians, 96% of all respondents said that airway pressure levels influenced their choice of tidal volumes[1]. However, the specific pressure limits used for this purpose were not included in the survey. There was considerable discussion of the pressure limit for our traditional study group in 1995, while ARDSNet investigators were designing Study #01. The pressure limit of 50 cm H_2O was selected by consensus, based on the ARDS Network investigators' personal experiences, observations of their colleagues' practices, and with input from practicing physicians at some of the ARDS Network centers. Our selection of 50 cm H_2O as the plateau pressure limit for this group is consistent with other experts' consensus on this question. In 3 of the 4 other randomized trials of tidal volume reduction in ALI/ARDS, the investigators used the following inspiratory pressure limits selected for the higher tidal volume study group protocols: peak inspiratory pressure of 60 cm H_2O [34], peak inspiratory pressure of 50 cm H_2O [35], and plateau pressure of 45-55 cm H_2O [23]. As in ARDSNet Study 01, these pressure limits were carefully selected to represent a mainstream approach in which the clinical objectives of maintaining gas exchange and breathing comfort have higher priority than the objective of preventing lung injury from overdistention. (In the fifth trial, the higher tidal volume study group protocol did not include an inspiratory pressure limit [37].) The inspiratory pressure limit

of 50 cm H_2O was considered appropriate by the independent protocol review board, the independent DSMB, and the institutional review boards.

Rationale for the 6 ml/kg protocol

There were several reasons for selecting the target tidal volume of 6 ml/kg PBW for the lower tidal volume study group in ARDSNet Study 01. 1) In two notable case series reports, low mortality rates were reported in ARDS patients who received tidal volumes of 4-7 ml/kg [3, 4]. 2) Promising results were also reported in a preliminary report of a small randomized trial in a study group in which the targeted tidal volumes $\leq$ 6 ml/kg [16]. 3) A report by Lee et al suggested that use of tidal volumes of 6 ml/kg would yield better clinical outcomes than use of tidal volumes at 12 ml/kg [22]. 4) A phase II clinical trial of higher versus lower tidal volume ventilation in ARDS was being conducted at one of the ARDS Network centers from 1994-1996 [23]. In that study, patients randomized to the lower tidal volume group received an initial tidal volume of 8 ml/kg PBW. This was subsequently reduced if plateau pressures exceeded 30 cm of H_2O. Physiologic data from patients who had completed this study were available to ARDS Network investigators while designing ARDSNet Study 01. There was little hypercapnia in the first five days after tidal volume reduction in this study. Effects on acid-base balance were also mild. These data suggested that ventilation with tidal volumes of $\leq$8 ml/kg predicted body weight were safe. The favorable experiences reported by Hickling et al [3, 4], Amato et al [16], and Lee et al [22] strongly suggested that further reductions in tidal volumes and plateau pressure could be beneficial.

There are several reasons why we selected an inspiratory airway plateau pressure = 30 cm H_2O as the pressure limit in the ARDSNet Study 01 lower tidal volume group. 1) In two encouraging uncontrolled case series reports of lower tidal volume ventilation [3, 4], tidal volumes were adjusted downward if peak inspiratory pressures exceeded 30-40 cm H_2O. 2) Some animal studies suggested that there was little-no injury when peak airway pressures were <30 cm H_2O but that injury occurred when airway pressures exceeded 30 cm H_2O [13, 14, 38-40]. 3) When normal humans inspire voluntarily to a maximum lung volume (total lung capacity), transpulmonary pressure is approximately 30 cm H_2O [41]. This suggests that inspiratory alveolar pressures of 30 cm H_2O could be safe. 4) In 1993, an American College of Chest Physicians consensus conference on mechanical ventilation recommended using an inspiratory plateau pressure limit of 35 cm H_2O [7]. 5) An inspiratory pressure limit of 30 cm H_2O was used in a phase II trial of lower tidal volume ventilation in ALI/ARDS at one of the ARDS Network sites in 1995 [23]. An interim DSMB analysis for one of this study indicated no safety concerns.

The reports by Hickling et al, Amato et al, and Lee et al [3, 4, 16, 22] suggested that 6 ml/kg would be safer than higher tidal volumes such as 7, 8, 9, 10, and 11 ml/kg. On the other hand, other studies demonstrated that ventilation with higher tidal volumes was better for achieving important physiologic objectives, including maintenance of gas exchange and acid-base homeostasis, especially in acutely injured lungs [8-10, 42]. This suggested that ventilation with tidal volumes of 12 ml/kg would yield better outcomes than ventilation with tidal volumes of 7-11 ml/kg. It was necessary to conduct our study to provide evidence for the superiority of either approach with respect to their effects on important clinical outcomes such as mortality.

OHRP asked if there was any basis pre-study to assume that these two experimental groups (with target tidal volumes of 6 and 12 ml/kg PBW) would be safer and more effective than tidal volumes ranging from 7 to 11 ml/kg PBW. For reasons given in response to issue A.(1)(b), we had ample reason to think that risks to study participants were not increased relative to the risks associated with routine care treatment. With respect to a theoretical study protocol in which the targeted tidal volume was somewhere in the range of 7 to 11 ml/kg PBW, there were strong opinions and arguments favoring both traditional and lower tidal volume approaches, and the strengths of these opinions were approximately equal. The critical care community was in equipoise on this issue. We did not know which approach (prioritization scheme) would yield better outcomes. Therefore, we had no basis pre-study to assume that either 6 or 12 ml/kg PBW was safer or less safe than any targeted tidal volume in the range of 7 to 11 ml/kg PBW.

OHRP asked if the tidal volumes for the two experimental groups were selected based on the expectation that this would increase the likelihood of showing a statistically significant difference between the two experimental groups. We suspected that *if* the lung-protective approach was more favorable, then the beneficial effect of reducing tidal volume and inspiratory pressure would be a continuum, spanning wide ranges of tidal volumes and pressures. We also suspected that *if* the gas exchange/breathing comfort approach was more favorable, that the effect of higher tidal volumes and inspiratory pressures would be a continuum, spanning wide ranges of tidal volumes and pressures. Therefore, if either approach was preferable, then a trial that compared tidal volumes of 12 vs. 6 ml/kg was more likely to show statistically significant differences than a trial with a smaller difference between study group tidal volumes. However, the reasons for selecting targeted tidal volumes 12 ml/kg and 6 ml/kg PBW (and inspiratory plateau pressure limits of 50 and 30 cm H_2O) were as explained in the previous paragraphs of section A.(5). We did *not* select the tidal volumes and inspiratory pressure limits in the study group to increase the likelihood of showing statistically significant differences.

(6) Did the ARDSNet investigators take into account any animal studies assessing the mortality rate of animals assigned to multiple different tidal volumes over a wide range of tidal volumes? If so, please provide relevant literature. If not, did the ARDSNet investigators consider conducting such animal studies before initiating the clinical trial in humans?

ARDSNet investigators know of no studies that assessed mortality rates of animals assigned to multiple different tidal volumes over a wide range of tidal volumes. Some experiments in animal models suggested that there was a continuum of lung injury as tidal volumes and inspiratory pressures are increased over a wide range [14, 40]. However, these experiments were relatively brief (minutes to hours in duration) because the experimental models cause progressive respiratory failure and circulatory collapse within a short time. Therefore, the models cannot be used to determine if beneficial effects of lower tidal volume ventilation on mortality outweigh the adverse effects of this approach.

ARDSNet investigators did not consider conducting such animal studies before initiating ARDSNet Study 01 because the experimental models would not allow clinically relevant assessments of effects on mortality of mechanical ventilation with different tidal volumes. On the other hand, there was a substantial and growing body of evidence in the previously cited reports by Amato et al [16], Hickling et al [3, 4, 16], and Lee et al [22] that indicated that ventilation with lower tidal volumes could be beneficial. A phase II clinical trial was being

conducted at one of the ARDS Network centers in 1994-1995, when the ARDSNet Study 01 was designed [23]. A Data and Safety Monitoring Board report from this trial, conducted in 1995, indicated no safety concerns. We believed that a definitive phase III clinical trial was indicated. Our protocol review committee, DSMB, and IRBs agreed.

(7) Please provide evidence from the ARMA study, or any other human studies, that supports the conclusion that a tidal volume of 6 ml/kg PBW is safer or more effective than a tidal volume of 7, 8, 9, 10, or 11 ml/kg PBW. Is it possible that tidal volumes of 7-11 ml/kg, where plateau airway pressures are maintained at a level less than or equal to 30-35 cm H_2O, could be equally safe or safer? In providing your response, please note that the IRB-approved ARMA protocol provided a theoretical basis for why tidal volumes of 6 ml/kg PBW may have posed greater risk of harm and discomfort in comparison to use of higher tidal volumes that are less than 12 ml/kg PBW, but limit the level of plateau airway pressure. These included an increased probability of developing hypercapnia, respiratory acidosis (requiring more sodium bicarbonate), volume overload, hypernatremia, agitation and dyspnea (requiring greater sedation), and oxidant-induced lung injury secondary to higher FiO_2 requirements.

ARDSNet Study 01was not designed to demonstrate that the lower tidal volume protocol, with a targeted tidal volume of 6 ml/kg PBW, was safer or more effective than a tidal volume of 7, 8, 9, 10, or 11 ml/kg PBW. However, analysis of the ARDSNet Study 01 data base strongly suggests that ventilation with tidal volumes of 6 ml/kg *is* safer than with tidal volumes in the range of 7-11 ml/kg. A smoothed plot of mortality versus plateau pressures on the first day after randomization in ARDSNet Study 01 is shown in Figure 7. The positive slope of this

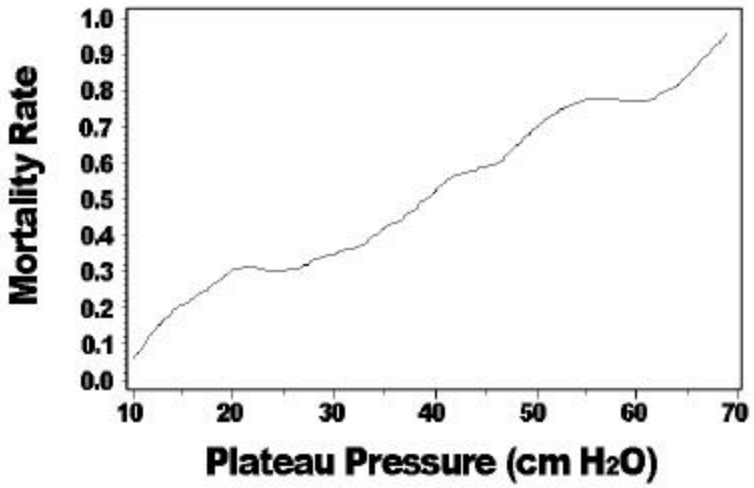

Figure 7: Smoothed plot of mortality versus inspiratory airway plateau pressure on Day 1 of mechanical ventilation in ARDSNet Study 01. Patients in both the traditional and lower tidal volume study groups are represented on this graph

relationship primarily reflects greater risk of mortality in patients with lower respiratory system compliance (low respiratory system compliance is a marker of disease severity). However, in a logistic regression analysis, plateau pressure independently predicted mortality when APACHE

III (which reflects disease severity, [43] and tidal volume were held constant. When plateau pressure and APACHE III were held constant, tidal volume was not an independent predictor of mortality. These observations suggest that effects of different tidal volumes (raising or lowering) are mediated through the associated effect on plateau pressures. Importantly, there is no diminution or reversal of the beneficial effects of lowering plateau pressures within the range of plateau pressures that occurred in ARDSNet Study 01. These data strongly suggest that tidal volumes of 7-11 ml/kg, with plateau pressures maintained at levels < 30-35 cm H_2O, *are not* as safe as tidal volumes of 6 ml/kg, with plateau pressures that would be even lower. They strongly suggest the opposite: *lower tidal volumes with resulting lower plateau pressures are safer.*

Consider also the data shown in following table, which are taken from ARDSNet Study 01.

		Day 1 P_{PLAT} Quartiles (P_{PLAT}'s in cm H_2O)			
		1	2	3	4
V_T 12 ml/kg Group:	P_{PLAT} Range	$\leq$26	26-31	32-37	>37
	Mortality (%)	34	33	39	56
V_T 6 ml/kg Group:	P_{PLAT} Range	$\leq$20	20-25	25-29	>29
	Mortality (%)	23	30	33	45

The table shows plateau pressures and mortality rates for quartiles of patients defined according to plateau pressures (each quartile in each study group contains 25% of the patients in the study group on day 1). The plateau pressures in the first and second quartiles of the 12 ml/kg study group are all $\leq$ 31 cm H_2O. The combined mortality rate for these first two quartiles in the 12 ml/kg study group was 34%. The plateau pressures in the 1st and 2nd quartiles in the 6 ml/kg study group were lower than in the corresponding two quartiles in the 12 ml/kg study group because the tidal volumes were lower. The mortality rate in the combined 1st and 2nd lower tidal volume study group quartiles was 27%. *Thus, it appears that among patients whose plateau pressures were $\leq$ 31 cm H_2O while receiving tidal volumes of 12 ml/kg, mortality would have been lower if their plateau pressures had been lowered further by decreasing tidal volumes to 6 ml/kg.*

We know of no other credible data that address the question posed by the OHRP, "Is it possible that tidal volumes of 7-11 ml/kg…could be equally safe or safer." Because the table above contains data from subsets, we must be conservative with any inferences drawn from the comparisons. However, the sizes of the subsets are substantial (over 200 patients in the combined 1st and 2nd quartiles in each study group; 430 patients total). Moreover, the subsets were defined in direct relation to the key physiologic variable of interest and over the range of interest (plateau pressures < 32 cm H_2O). No patients were removed from this analysis except those in whom the required data were not available. We know of no reason why there would be any bias in the patients on whom data were not available in the two study groups.

(8) For each individual subject for whom informed consent was obtained and documented, please provide the following information in tabular or spreadsheet format:

Requested data elements that are available in the ARDSNet CCC database have been provided on the included CD in tab delimited .txt files suitable for import into Excel or other spreadsheet or database applications. To open a .txt file in Excel, right click on the file,

highlight "Open With" and select Excel from the menu. The baseline and outcome data requested in items (a), (c), (d), (f), (g), and (i) is included in the file `arma\data\ohrp_arma_baseline_outcome.txt.`

For item (b) please see file `arma\ic_withdrawal_data\arma_ic.xls.`

The on study data requested in item (h) is included in the file `arma\data\ohrp_arma_on_study.txt.`

For item (j) please see file `arma\ic_withdrawal_data\arma_wthdrw.xls.`

An additional file, `arma\data\ohrp_arma_data_dictionary.txt,` is a data dictionary which fully describes the structure of each of the tab delimited data files. Simple summary statistics for all data elements are provided in Appendix D.

(a) Site of enrollment.

See file `arma\data\ohrp_arma_baseline_outcome.txt`

(b) Date informed consent was obtained and documented.

See file `arma\ic_withdrawal_data\arma_ic.xls`

(c) Number of consecutive days on mechanical ventilation prior to enrollment in the clinical trial.

See file `arma\data\ohrp_arma_baseline_outcome.txt`

(d) Predicted (or ideal) body weight.

See file `arma\data\ohrp_arma_baseline_outcome.txt`

(e) For each day the subject was on mechanical ventilation prior to randomization, up to a total of 7 consecutive days moving back in time, please provide the mode of mechanical ventilation, tidal volumes used, and plateau airway pressures measured.

Pending chart review at sites.

(f) If the subject was not randomized, an explanation as to why randomization did not occur. For each randomized subject, identify the experimental group to which the subject was assigned.

All subjects who gave informed consent were subsequently randomized .

(g) The following baseline data: age, gender, APAHCE III score, tidal volume, plateau airway pressure, peak inspiratory pressure, PEEP, FiO_2, PaO_2, pCO_2 and arterial pH.

See file `arma\data\ohrp_arma_baseline_outcome.txt`

(h) The following data for days 1, 3, and 7 post randomization: tidal volume, plateau airway pressure, PEEP, FiO_2, PaO_2, pCO_2 and arterial pH.

See table `arma\data\ohrp_arma_on_study.txt.`

(i) All measured outcomes variables or study endpoints, including death before discharge, day post randomization when death occurred, breathing without assistance and day on which this occurred, number of ventilator-free days (days 1 to 28), barotrauma (days 1 to 28), and number of days without failure of nonpulmonary organs or systems (days 1 to 28).

See file `arma\data\ohrp_arma_baseline_outcome.txt`

(j) With respect to the outcome variables, please include whether any subject was withdrawn from the study, the date of withdrawal, and the reason for withdrawal (including withdrawal of consent by the subject or the subject's legally authorized representative, withdrawal by treating physician, protocol violation, or other reason). Please specify how subjects who withdrew from the study after randomization were handled in the data analysis.

These subjects were included in the data analysis. We adhered to the "intent to treat" principle. See file `arma\ic_withdrawal_data\arma_wthdrw.xls` on the included CD.

(9)OHRP is aware that the research protocol was amended at several of the participating ARDSNet sites to allow for collection of clinical and outcome data on all patients who were screened for participation in the clinical trial, but were not enrolled either because they refused participation or met exclusion criteria. Please provide a complete summary of data collected on all such patients.

The data collected for the screened but un-enrolled patients is included in the tab delimited file `arma\data\ohrp_arma_screen.txt`. The structure of this file is also found in the data dictionary `arma\data\ohrp_arma_data_dictionary.txt` and summary statistics are included in Appendix D. In addition the data entry screen for this form with the field names written in is included in Appendix E. An analysis of the un-enrolled patients is provided as an appendix to the December 9th, 2002 FACTT DSMB report included in Appendix K.

(10) Please provide a copy of all publications, abstracts, and manuscripts related to the ARMA trial, including those publications, abstracts, and manuscripts related to data collected on patients who were screened for participation in the clinical trial, but were not enrolled either because they refused participation or met exclusion criteria.

See Appendix F

(11) The enclosed complaint letter alleges that the clinical trial should have been stopped earlier, given the p value of 0.007 for the difference between the two experimental groups in the primary outcome measure, mortality rate. OHRP also notes that the p values for differences between the two experimental groups for three other main outcome variables (breathing without assistance by day 28; number of ventilator free days, days 1 to 28; and number of days without failure of nonpulmonary organs or systems, days 1 to 28) were equal or less than 0.007. Furthermore, OHRP notes that the IRB-approved protocol included a plan for interim analyses at 200, 400, and 800 subjects, but the study was stopped after a fourth interim analysis at an enrollment of 861 subjects. As a result, OHRP is concerned that (i) the study was not adequately monitored; (ii) the plan for monitoring provided for under the IRB-approved protocol was not followed; and (iii) these failures in monitoring may have resulted in preventable subject deaths in the subjects randomized to the higher tidal volume experimental group. Please respond in detail. Please address the following in your response:

Provide the statistical plan for the interim analyses.

The study was designed to be reviewed when the study had an effective sample size (defined below) of 200, 400, 600, 800 and 1000. We used a plan developed by DeMets and Ware [44]. The plan involves stopping and finding the 6ml/kg group to be superior if the two

sided p-value in favor of that group was 0.000006, 0.00014, 0.0009, 0.0024, 0.043, after 200, 400, 600, 800 and 1000 patients respectively. The trial would stop for futility if the p-value in favor of 12 ml/kg was less than 0.4389 at 200 patients, less then 0.9853 on 400 patients, or the p-value in favor of 6 ml/kg was greater than 0.68 at 600 patients or 0.46 at 800 patients.

Note that the trial was designed to continue despite the fact that the p-value was less the 0.05. This is necessary because if a trial is stopped as soon as the p-value reaches 0.05 then the probability of a false positive trial is greater then 5% [45]. For instance if we had stopped when the p-value was first under 0.05 in the five interim analyses then we would have a 14% chance of stopping and declaring that 6ml/kg was superior even if the two treatments had the same mortality rate. The reason for this is that although the probability is 0.05 at each look at the data, there are five looks at the data so the total probability of declaring a false positive result at any of those looks is greater than 0.05. If we looked at the data after every patient and stopped when the p-value became 0.05 than we would have nearly a 50% chance of stopping and declaring that 6ml/kg was superior under the null hypothesis that the treatments did not differ. The method that we used is termed a Group Sequential Clinical Trial and is standard methodology for large clinical trials with mortality as an endpoint. It is suggested for pharmaceutical trials by the Food and Drug Administration [46].

An asymmetric plan was used because after the first few patients it was clear to the investigators that 12 ml/kg was much better tolerated than 6 ml/kg, so that if the two were equivalent 12 ml/kg would be the treatment of choice. Thus there was no need to prove that 12 ml/kg was superior. In an asymmetric design the stopping boundaries are different for stopping the trial if 6ml/kg is better than they are for stopping the trial if 12ml/kg is better. In the table below only the two sided stopping p-values to show the superiority for 6ml/kg are shown. The one sided p-values to stop if 12mg/kg were better are 0.2194, 0.4926, 0.6616,0.7688 and 0.8394. Most of the other published ventilator trials also used an asymmetric design.

The primary endpoint was the hospital mortality rate at 180 days. At interim looks at the data there would be patients who where still hospitalized and would not have met a study endpoint. Thus actuarial methods were used to estimate the 180 day mortality [47]. Since some patients only provide partial information to this estimate, the precision of the estimate will be smaller than the precision of an estimate based on complete data. The effective sample size at each interim analysis is the number of patients with complete data who would be required to provide the same precision to the estimate of the 180 day mortality that was observed [48].The effective sample size will always be smaller than the actual sample size at each interim analysis.

Since meetings of the Data and Safety Monitoring Committee (DSMC) were scheduled two to three months in advance we were never able to analyze the data at exactly the times described in the monitoring plan. We used a procedure suggested by Lan and DeMets [49] to adjust the stopping values when the interim analysis did not occur at exactly the specified times. This is also a standard procedure in clinical trials.

The table below shows the date of each interim report, the actual and effective sample size, the estimated mortality rates and the p-value for the comparison. Data is also presented on the vent-free day comparison and other secondary endpoints. The statistical tests for mortality were based on the difference in 180 day mortality divided by the standard error of the difference. The other endpoints were compared using a Wilcoxon test.

(b) Provide the outcome of each interim analysis by the DSMB. Please provide the following: date of the DSMB review; number of subjects enrolled at the time of review; summary data for each review including number of subjects enrolled in each experimental group; endpoints reached for each primary and secondary endpoint; and statistical tests used and p values for the comparison of each endpoint measurement between the two experimental groups.

Date of DSMB review:		12/05/1996	10/15/1997	04/22/1998	03/02/1999
Enrollment	6 ml/kg	105	234	317	422
Enrollment	12 ml/kg	101	236	309	419
Effective sample size		183.4	450.6	605.9	796.3
180 day mortality	6 ml/kg	24.95 ± 6.41	30.01± 3.04	30.76 ± 2.64	30.44± 2.31
180 day mortality	12 ml/kg	43.94 ± 7.26	41.67± 3.28	40.02 ± 2.81	39.78 ± 2.44
	P-value	0.00275	0.0091	0.0163	0.0054
Stopping P-value		6.2E-06	0.0034	0.009	0.024
Vent Free days	6 ml/kg	15	12	14	13
Vent Free days	12 ml/kg	0	5	5	6
	P-value	0.0004	0.0149	0.0151	0.0087
Organ Failure Free days:					
Cardiovascular	6 ml/kg	Not reported	23	24	23
	12 ml/kg	Not reported	19	21	20
	P-value	Not reported	0.0044	0.0247	0.0071
CNS	6 ml/kg	Not reported	14	14	14
	12 ml/kg	Not reported	7	12	13
	P-value	Not reported	0.0222	0.2318	0.3791
Coagulation	6ml/kg	Not reported	26	25	26
	12 ml/kg	Not reported	23	24	24
	P-value	Not reported	0.0049	0.0925	0.0145
Hepatic	6 ml/kg	Not reported	25	25	25
	12 ml/kg	Not reported	17	20	19
	P-value	Not reported	0.1004	0.243	0.0487
Pulmonary	6 ml/kg	Not reported	1	1	0
	12 ml/kg	Not reported	0	0	0
	P-value	Not reported	0.0847	0.1939	0.3114
Renal	6 ml/kg	Not reported	28	28	28
	12 ml/kg	Not reported	20	25	25
	P-value	Not reported	0.0102	0.1017	0.0076

Table 1: Dates, actual and effective sample sizes, mortality (+/-SEM), and actual vs. protocol specified P values for stopping are given for each DSMB review of ARDSNet Study 01 (ARMA). Median ventilator free and organ failure free days are also given for each DSMB review.

(c) With each subsequent interim analysis by the DSMB, was any trend noted that would have allowed one to predict when the difference in mortality between the two experimental groups would have reached scientific statistical significance at a p value of 0.05?

The DSMB did not attempt to predict when the p-value would have reached statistical significance at p=0.05, they did not note any trend, nor did they contemplate changing the frequency of interim analyses. As we explained previously, stopping the trial when it reached statistical significance at p=0.05 is not a statistically valid procedure. Increasing the frequency of interim analysis would have required a lower p-value for stopping and would not have appreciably reduced the number of patients treated on the clinical trial.

(d) Please clarify the point (by date and subject number) during the course of the study at which the difference in mortality rates between the two experimental groups reached a p value of 0.05.

In response to question 11(d). We calculated the date at which the trial first reached statistical significance at p=0.05. This was done retrospectively based on our data files, no such calculation was done during the trial. The trial first reached significance on 08/20/96, at that time there were 123 patients enrolled. Note that stopping the trial at the first time that a 5% value was reached would not be a statistically valid procedure because the probability of a false positive result would be much higher than 5% in fact it would be close to 50%.

(e) Was an increase in the frequency of the DSMB interim analyses ever considered or recommended during the course of the clinical trial?

See above section (c).

(f) If a DSMB interim analysis was planned after 800 subjects were randomized, why was enrollment stopped after 861 patients were randomized? On what dates were the 800th and 861st subjects enrolled? On what date was the study discontinued?

The study stopped when 861 patients were enrolled on 03/10/99 a time when the effective sample size was 796. The 800th patient was enrolled on 12/15/98. However this was according to the analysis plan. At 12/15/98 the effective sample size would have been far less than 800, the trial was designed to have an interim look at an effective sample size of 800 not an actual sample size of 800, as described in the ARDSNet Study 01 protocol.

(12) OHRP is concerned that the ARMA protocol provides little substantive discussion of the multiple complex ethical issues related to human subject protections that are presented by such research. For instance, the protocol does not describe, among other things, the following:

(a) justification for an informed consent process that involves surrogate consent for research involving greater than minimal risk and presenting possibly limited benefits to the subjects"

Local IRBs have the responsibility to make independent determinations on these difficult issues and therefore may have their own site specific responses to these issues.

What follows are the opinions of the ARDSNet Clinical Network on the issues raised in this item.

In contrast to the existence of special regulations involving children, the federal regulations do not provide a hierarchy of research categories establishing more rigorous substantive and procedural standards for proposals presenting more than minimal risk to decisionally incapable subjects. However, the general view for adults is that it is permissible to include incapable subjects in potentially beneficial research projects as long as the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting[50]. This standard is similar to the general demand for clinical equipoise when human subjects participate in clinical trials[51]. Several U.S. task forces have deemed it is permissible to include incapable subjects in greater than minimal risk research as long as there are the potential for beneficial effects. 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."[52] The Maryland draft legislation deems "expected medical benefit" research permissible if an agent or surrogate, "after taking into account treatment alternatives outside of the research, …concludes that participation is in the individual's medical best interest."[53] 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…"[54]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research, we believe that the ARMA trial presented a balance of risks and expected direct benefits that is *similar* to that available in the clinical setting. As such, we disagree with OHRP's interpretation that the ARDSNet Study 01 (ARMA) trial involved greater than minimal risk and presenting "possibly limited benefits" to the subjects. Essentially, OHRP's interpretation is that the balance of risks and benefits in the ARDSNet Study 01 (ARMA) trial was greater than that available in the clinical setting.

The existing federal research regulations (45CFR46) acknowledge the possibility of proxy consent through the use of legally authorized representative (LARs) [55]. According to NBAC, an investigator should accept as an LAR…a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place [54]. Finally, OHRP has opined in its 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 [56].

(b) additional safeguards that were included for subjects who were likely to be vulnerable to coercion or undue (e.g., independent consent monitors);

The ARDSNet Study 01 (ARMA) research involved subjects who might be vulnerable to coercion or undue influence. Although not stated in the protocol, as required in 45CFR46.111(b) additional safeguards were included to protect the rights and welfare of

these subjects. These safeguards were outlined by the individual IRBs in a previous OHRP inquiry. Please let us know if additional clarification is needed.

(c) for subjects for whom consent would be initially obtained from a family member, a description of the procedure that would be followed for obtaining and documenting informed consent from those subjects who subsequently became capable of consent for themselves during the course of the trial;

Since the conclusion of the ARDSNet Study 01 (ARMA) trial, the ARDSNet surveyed its member sites on whether there was a process in place for obtaining informed consent from subjects who were initially enrolled via surrogate consent and subsequently became capable of providing consent for themselves during the course of the trial. The results of this survey are presented below in the responses to ARDSNet Study 05 (FACTT) issues.

(d) the basis for excluding pregnant women.

The administration of a tidal volume of 6ml/kg might lead to permissive hypercapnia. Since the effects of increased levels of carbon dioxide on the developing fetus is not known, to minimize risks associated with this research study, it was recommended that pregnant women be excluded from participation.

(13) Regarding the informed consent document, OHRP has the following concerns:

(a) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, the following information, among other things, shall be provided to the subject or the subject's legally authorized representative: an explanation of the purpose of the research, the expected duration of the subject's participation, and a description of the procedures to be followed, and identification of any procedures which are experimental.

> ***(i) OHRP is concerned that the IRB-approved informed consent documents at most participating ARDSNet sites may have failed to adequately describe the purpose of the research. Instead of stating that the purpose of the study was to compare the effectiveness of two standard ways of inflating a patient's lungs, it appears that it would have been more appropriate to state that the main purpose of the study was to find out if patients with ALI/ARDS are have a higher or lower death rate when lungs are inflated with a low tidal volume (6ml/kg PBW) versus a high tidal volume (12 ml/kg PBW).***

Individual IRBs will need to comment on site-specific informed consent forms. The following response refers to the model consent form developed by the ARDSNet Ethics Committee.

The major objective of the ARDSNet Study 01 (ARMA) study was to compare the efficacies of two ventilation strategies in reducing *mortality* and *morbidity* in patients with acute lung injury. Accordingly, the first primary efficacy variable was "percentage of patients alive with unassisted breathing at hospital discharge." The second primary efficacy variable was "number of days of unassisted breathing." Because there were several objectives of the study, involving mortality *and* morbidity, the "broad" phrase "to compare the effectiveness" was used. To be sure, we agree that giving potential subjects specific information on the "main purpose" of the study is warranted. We respectfully disagree, however, with language suggested by OHRP, because a) it only states one of the primary objectives of the study and

b) use of the passive voice does not state explicitly the link between the use of the different ventilator strategies and their potential effects on mortality and morbidity.

(ii) OHRP is concerned that the IRB-approved informed consent documents at most participating ARDSNet sites may have failed to adequately describe the nature of the experimental design and the differences between the experimental interventions and standard ventilator management (which is listed as the alternative to participation in the research in several of the IRB-approved informed consent documents).

We agree that while the two tidal volumes used in the ARDSNet Study 01 (ARMA) trial reflected standard tidal volumes, the particular ventilator "strategies" were "experimental" in the sense that such strategies were modified from protocols used in other trials of lung protective strategies and thus included consensus driven expert recommendations.
We would like to point out while the ventilator strategies were "experimental", none of the specific components or interventions contained in the strategies were experimental. Finally, regarding the interests for human subject protections, we would like to point out that many of the procedures contained in the individual ventilator strategies were designed to minimize the risks of this study. For example, the procedures to maintain the pH below 7.45 and above 7.30 units; procedures to maintain the maximum plateau pressure in the 12 ml/kg group below 50 cm H20; procedures to ensure that the minimum tidal volume in both groups will be 4 ml/kg; and the procedures to ensure that PO2 in both groups are maintained above acceptable levels.

We appreciate the fine distinctions being made by the OHRP and will be more cognizant of such distinctions when we develop sample consent forms for future studies.

(iii) OHRP is concerned that the IRB-approved informed consent documents at most participating ARDSNet sites may have failed to adequately describe the duration of the study. The study involved collection of identifiable private information for up to 180 days after enrollment, whereas most of the informed consent documents indicated that the research would last for 28 days.

We agree that several of the informed consent documents incorrectly described the duration of the study. Included as part of one of the basic elements of informed consent is "the expected duration of the subject's participation." A study performed by one of the ARDSNet investigators showed that there is variability with the inclusion of these basic elements of informed consent in IRB-approved consent forms[57]. To reduce such variability, the ARDSNet adopted a "central review" mechanism of IRB-approved consent forms that is performed by the ARDSNet Ethics Committee. This mechanism is described in Appendix G. Essentially, the ethics committee reviews each consent document to ensure the inclusion of all of the basic elements of informed consent. This central review mechanism is not aimed at evaluating the language in the informed consent documents, as the inclusion of appropriate language is a function of each individual IRB. However, the accuracy of the subject's study duration is reviewed by the Ethics Committee.

(b) HHS regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent, a description of any reasonably foreseeable risks or discomforts to the subject shall be provided to the subject or the subject's legally authorized representative. OHRP is concerned that the IRB-approved informed consent documents at most participating ARDSNet sites may have failed to include death as one of the risks of the research.

The federal regulations state in 45CFR46.111(a):

> "In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)."

Subjects enrolled in the ARDSNet Study 01 (ARMA) trial would have received mechanical ventilation even if not participating in the research and could have received either 6 ml/kg or 12 ml/kg if not participating in the research. To be sure, outside of the study, the subject could have received a tidal volume selected from anywhere along a range of tidal volumes between 5 ml/kg to 15 ml/kg. We agree, however, that compared to what the subject could have received outside of the study, the chances of receiving 6 ml/kg or 12 ml/kg is higher by participating in the study. Accordingly, the act of being randomized to receive either 6ml/kg or 12 ml/kg might affect the possibility of a subject receiving a tidal volume that is associated with a different risk of death from what he or she might have received if he or she did not participate in the study. However, to merely state that "death is a risk of participating in the research" is an oversimplification of this complex issue, which could confuse and mislead the subject.

B. Concerns, questions, and allegations regarding the FACTT trial (ARDSNet Study #05):

(1) OHRP is concerned that the requirements of 45 CFR 46.111(a)(1) and (2) have not been satisfied for the FACCT (sic) trial. In particular, OHRP notes the following:

(a) Prior to designing the study and defining the experimental and control group interventions, the ARDSNet investigators appear to have failed to define in a systematic manner the specific range and frequency of target levels of central venous pressure (CVP) and pulmonary artery occlusion pressures (PAOP) on which patients were maintained during routine clinical practice at the participating ARDSNet study sites.

Prior to designing ARDSNet Study 05 (FACTT), the ARDSNet investigators extensively reviewed the issues of fluid management in ARDS, with respect to both the published literature and the available prior experience at the participating ARDSNet study sites. After an extensive literature search, no single published "evidence-based practice" could be identified, either with respect to fluid balance or vascular filling pressures. Much of this literature was recently summarized in a review of at least twelve studies which addressed management of fluids and vascular pressures in ICU patients [58]. These studies highlight the complex relationship between intravascular fluid volume and intravascular filling pressures, and demonstrate the highly variable practice patterns regarding these issues. Further evidence for the wide variability of routine clinical practice is found in the study of Carmichael, et al [1], which reported the results of a survey of physicians regarding their use

of the pulmonary catheter and the PAOP measurement in patients with ARDS. The indications for pulmonary artery catheter insertion were variable, and only one third of physicians advocated routine placement of the catheter in ARDS patients. When asked to provide an optimal PAOP, about 48% indicated a desire to maintain the PAOP between 11 – 15 mmHg, whereas another 50% indicated that 6 – 10 mmHg was optimal.

Among critically ill patients, some of whom had ARDS, a few published studies reported the benefits of a more "liberal" fluid administration in combination with other measures to increase oxygen delivery [59], but others reported improved outcomes with more constrained fluid management [60, 61]. In these studies, significant heterogeneity existed not only with regard to chosen goals, but also with respect to methods of achieving those goals.

In the absence of an evidence-based standard, the ARDSNet investigators sought further insight by examining the practice of fluid administration in their hospitals. In the nearly 900 patients enrolled in the ARDSNet Study 01 (ARMA) study (which had no specified protocol or guidelines regarding the management of fluids and intravascular pressures), there was tremendous variability in both daily fluid administration (range 1,059 ml to 13,696 ml per day), and cumulative net fluid balance (by day 4, cumulative net fluid balance [mean + or – standard deviation] was 4,728 +/– 9,389 ml). See Figure 8.

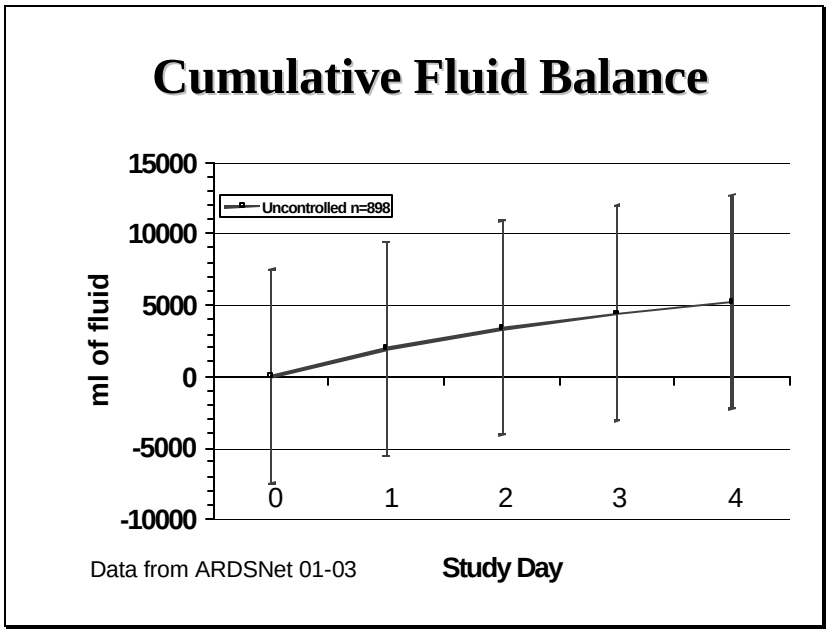

Figure 8: Cumulative fluid balance for 24 hours prior to entry (day 0) and study days 1-4 are given for 898 subjects enrolled in ARDSNet Studies 01 and 03.

No data regarding intravascular filling pressures in ARDSNet Study 01 (ARMA) patients are available, and we did not carry out a pre-study of CVPs and PAOPs actually measured at the ARDSNet centers in the treatment of the type of patients eligible for ARDSNet Study 05 (FACTT). The ARDSNet investigators recognized that there would be a large amount of

missing data, since pulmonary artery catheters are utilized in only a minority of such patients, and that clinical practice regarding measurement and recording of both CVPs and PAOPs is highly variable. It is widely recognized that intravascular pressure measurements are subject to significant acquisition errors, in the absence of a specific methodologies to obtain valid and consistent measurements [62, 63].Therefore, historical data obtained from the several ARDSNet intensive care units would be seriously flawed due to both missing data and a lack of standardized acquisition methodologies. In contrast, the ARDSNet Study 05 (FACTT) protocol and manual of operations includes specific guidelines and instructions regarding the acquisition of intravascular pressure measurements and assurance of their quality.

The controversies regarding fluid management strategies in ARDS, and the wide range of routine clinical practice, provided an imperative for the conduct of a controlled clinical trial to begin to answer the important questions related to these issues. In an editorial entitled "ARDS: The therapeutic dilemma", Hyers stated: "…the intriguing findings reported by these authors [61], coupled with results from animal studies, argues strongly for the conduct of a controlled clinical trial." Furthermore, a report of a combined NHLBI – FDA workshop identified acute lung injury as a priority area for investigating the role of the pulmonary artery catheter in affecting clinical outcomes [64]. Therefore, in designing and implementing ARDSNet Study 05 (FACTT), the ARDSNet investigators were clearly responding to a high priority need identified by clinicians, the scientific community and government agencies.

Designing a clinical trial to evaluate fluid management strategies in ARDS is confounded by the fact that no evidence-based practice exists. Thus, the task was to both develop and test reasonable management strategies as articulated by Marinelli: " furthermore, the optimal use of fluid and hemodynamic support remains controversial. Thus, controlled clinical trials are necessary to *develop* [italics added for emphasis] oxygenation, ventilatory, and hemodynamic support strategies which optimize recovery and minimize further injury and to define the role of injury…" [65]. The dual need to both develop and test fluid management strategies led the network investigators, after careful consideration, to design ARDSNet Study 05 (FACTT) as a combined phase II/III trial. Recognition of this design element is important to understanding the conceptual framework of ARDSNet Study 05 (FACTT).

(b) The ARDSNet investigators appear to have failed to provide sufficient justification for designing a pivotal phase III clinical trial that (I) included only two experimental arms defined by low target levels of CVP or PAOP in the fluid conservative experimental group and high target levels of COVP or PAOP in the fluid liberal experimental group, and (ii) excluded a control arm maintained on target CVP's or PAOP's from the middle of the normal range of these physiologic variables that may have been more representative of the levels of CVP and PAOP targeted most frequently during routine clinical practice at the time the study was initiated.

It is important to recognize, as stated above, that ARDSNet Study 05 (FACTT) is not simply a "pivotal phase III" clinical trial. Rather, ARDSNet Study 05 (FACTT) is designed as a study with both phase II and phase III components. As outlined above in the response to B. (1) (a), no evidence-based practice approach with regard to fluid and intravascular management for ARDS patients exists. Therefore, a conventional "control" group, with an explicitly defined protocol, could neither be identified nor utilized.

In view of this, the ARDS Network investigators did conduct extensive discussions regarding the appropriateness of including an arm of the trial in which there would be no attempt to manage fluid and catheter therapy. The decision not to include such a routine practice group rested upon the following considerations: First, the investigators believed that without explicit rules they would be unable to describe the practice of fluid management in the routine care group except in the most general of terms. Inability to precisely describe the intervention in this group severely limits its value as a comparator to the controlled groups. Regardless of whether the routine practice arm had "better" or "worse" outcomes it would be difficult to know why outcomes differed. Second, over time there may be changes, or "drift", in the practice of caring for patients in the routine care arm as a result of newly published information or merely changing attitudes. In this way, the routine care group would not receive a single style of care but many different and still indescribable styles over time. Specifically, there is risk that over time physicians caring for the routine care group would adopt some or all of the practices of the controlled group(s), perhaps even without realizing it (Hawthorne effect). Thus, the routine care group could have many interventions similar to the controlled participants but this contamination would be impossible to detect. Third, in general, the results of clinical trials comparing uncontrolled care to protocolized care are less compelling. This fact is evidenced by recent controversy over which elements, if any, of a treatment strategy accounted for benefits seen in a study of the early protocolized hemodynamic management of patients with sepsis [66] .Finally, the literature contains examples of important clinical trials comparing two protocolized treatments in which arguably neither treatment matched routine care, but both of which were well within the range of current routine practice. For example, a recent trial compared clinical outcomes in critically ill patients randomized to receive blood transfusions according to two different explicit protocols that utilized different schemes for prioritizing competing clinical objectives [32]. Before this study, physicians' standard practice transfusion practices were highly variable.

In view of this, the investigators chose to study two expert consensus management strategies that are reasonable and predicted to provide fluid balance and intravascular pressures that are well within the range of clinicians' currently widely variable routine practice. Then, this approach received vigorous scrutiny with regard to feasibility and safety in the initial phase II portion of the trial. As stated in the "Risk Assessment" portion of the protocol, "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." And, as identified in section 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." This process was carried out as designed, including full review by the independent DSMB following the phase II portion of ARDSNet Study 05 (FACTT).

The overview of patients during the phase II portion of the trial was intense and timely. During weekly conference calls of the investigators, <u>each</u> protocol assessment and

instruction, and the subsequent response of the patients, for the first 60 enrolled patients was reviewed in detail. The same oversight was provided to the first two patients, at least, that were enrolled at each participating hospital.

It should be emphasized also that the ARDSNet Study 05 (FACTT) protocol does not force patients into specific filling pressure ranges with regard to CVP or PAOP. Rather, the protocol utilizes fluid boluses or diuretics to move hemodynamically stable patients toward filling pressure targets, but several "checks and balances" are designed to attenuate or withhold such interventions if they could be considered unsafe or lack potential benefit. For example, a fluid bolus is not given (even if the filling pressure is below "target"), if the patient has a high oxygen requirement (safety issue) or has a high cardiac index (unlikely to achieve clinical benefit). *The protocols use individual patient measurements and responses to generate patient-specific, individualized, protocol instructions.*

A more complete listing of the protocol safeguards is provided below:

A) Patient assessments are required at least every 4 hours to detect and correct any hemodynamic abnormalities as quickly as possible. More frequent assessments can be conducted if deemed in the best interest of patient safety.

B) Intravascular pressure targets chosen as targets for fluid or diuretic administration for both liberal and conservative randomized patients are within routine practice ranges observed for ARDS patients not being managed with a fluid protocol, as evidenced by the baseline, pre-randomization values observed in the ARDSNet Study 05 (FACTT) patients (see subsequent discussion). No protocol instruction is designed to achieve a non-physiologic intravascular pressure target.

C) The protocol requires basic laboratory monitoring to provide the DSMB with data necessary to identify potential safety concerns. The primary physician may obtain any additional laboratory studies thought to be in the patient's best interest.

D) Selection of the fluid type (e.g. crystalloid, colloid or blood) is at the discretion of the primary physician. This rule recognizes that a variety of different fluid selections may be appropriate over time.

E) All protocolized fluid management is suspended for hypotensive patients. This assures that intercurrent problems, unrelated to the protocol, causing hypotension (e.g. gastrointestinal bleeding, sepsis) are rapidly identified and appropriately treated. In addition, this feature guarantees that if hypotension were the result of suboptimal intravascular volume (a theoretical risk for the conservative group) it would be corrected as rapidly as possible.

F) When a vasopressor or fluid bolus is administered, the protocol suspends diuretic instructions for at least 12 hours. This safeguard was designed to prevent oscillation between diuretic and fluid bolus or vasopressor therapy that could, in theory, result in repeated hypotension.

G) For patients randomized to the "liberal" strategy, the protocol suspends fluid administration when hypoxemia reaches a specific threshold unless there is a compelling reason to administer fluid (i.e. hypotension, oliguria, or low flow state accompanied by a lower intravascular filling pressure). In addition, when the

cardiac index is at a level sufficient to suggest that additional pre-load would not be beneficial, the protocol withholds fluid.

H) For all patients, the protocol limits the amount of fluid mandated to treat oliguria, low flow states, and low intravascular filling pressures. This limit varies by patient weight but typically represents about 50% of the mean daily fluid volume administered in the absence of a fluid protocol. The protocol, therefore, does not instruct the administration of fluid volumes in excess of those commonly used in practice. Because it is recognized there may be circumstances in which more fluid than instructed by protocol could be beneficial, the protocol allows, but closely monitors, additional fluid administration.

I) Diuretics are withheld and fluid boluses are administered in all situations where lower intravascular pressures are associated with hypotension, oliguria, or reduced flow in a specific patient. This rule is designed to minimize potential risks to conservative randomized patients even though it may reduce group separation.

J) For all patients, daily diuretic doses are limited to known safe levels to prevent drug toxicity.

K) Diuretic dosing is individualized to patient response. Low diuretic doses are used initially and similar doses are continued if there is an appropriate physiologic response. In the absence of response, doses are increased by safe increments and intervals to a maximum that falls well within clinical practice limits.

L) For all patients, diuretics are withheld if renal function indices suggest diuretics could be harmful or would likely be ineffective.

As a result of this protocol design, both the "conservative" and "liberal" ARDSNet Study 05 (FACTT) patient groups are managed on the ARDSNet Study 05 (FACTT) protocol with filling pressures that are well within the middle portion of the range of "baseline" values that were obtained prior to protocol implementation (and therefore fall within the middle of routine clinical practice), as illustrated in figures 9 and 10 below.

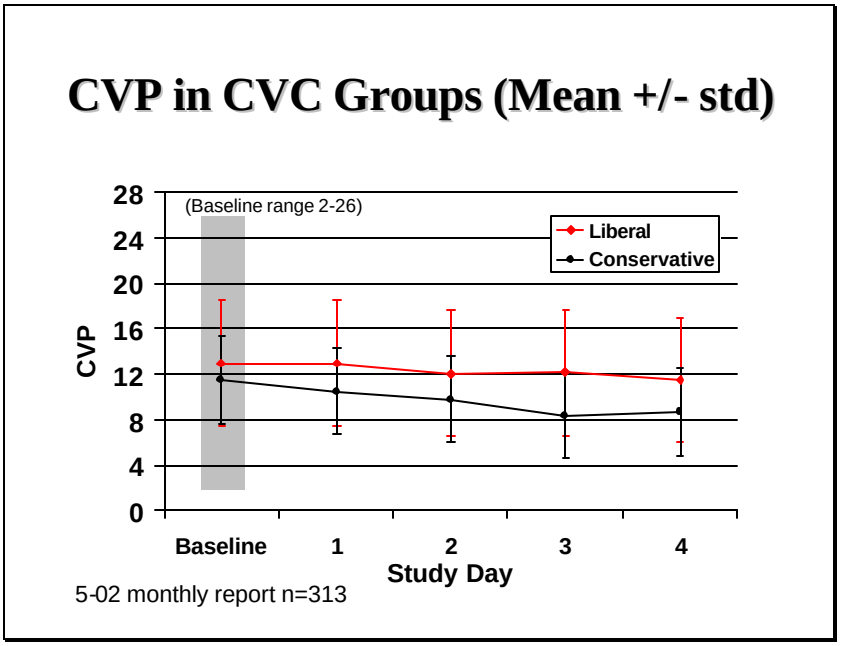

Figure 9: Central venous pressure (CVP) at baseline and on study days 1-4 in patients randomized to the central venous catheter (CVC) groups in FACTT. Grey bar indicates range for CVP prior to fluid management instructions (baseline).

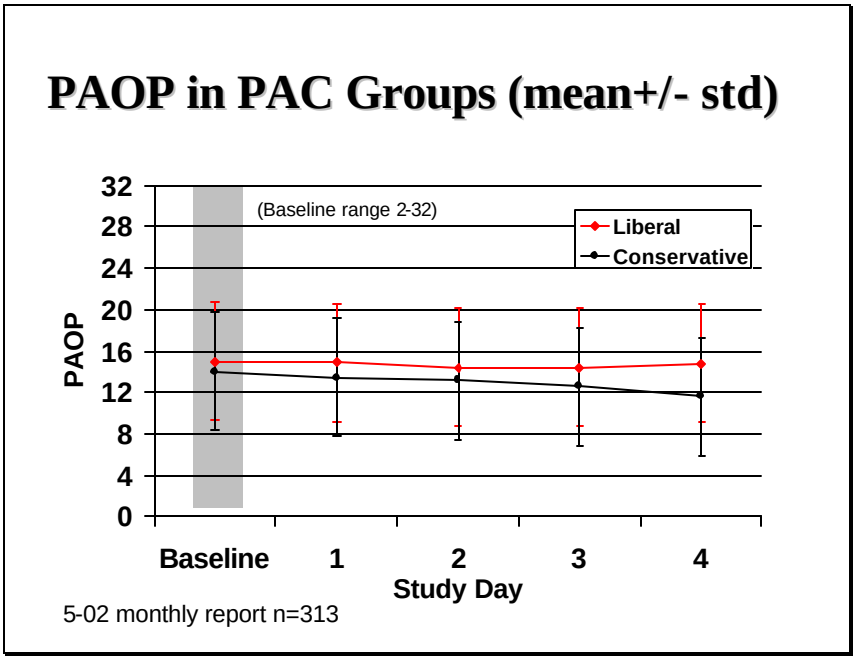

Figure 10: Pulmonary arterial occlusion pressure (PAOP) at baseline and on study days 1-4 in patients randomized to the pulmonary artery catheter (PAC) groups in FACTT. Grey bar indicates range for PAOP prior to protocol-specified fluid management instructions (baseline).

Therefore patients do not have very low levels of CVP or PAOP in the "conservative" experimental arm and very high levels of CVP or PAOP in the "liberal" experimental arm. In fact, most patients in both groups do fall in the "middle of the normal range of these variables that may have been more representative of the levels of CVP and PAOP targeted most frequently during routine clinical practice at the time the study was initiated." The cumulative net fluid balance in the "liberal" and "conservative" groups also fall within routine clinical practice (fluid balance observed in the ARDS Net #01 study, in which fluid balance was uncontrolled), as illustrated in figures 11 and 12 below.

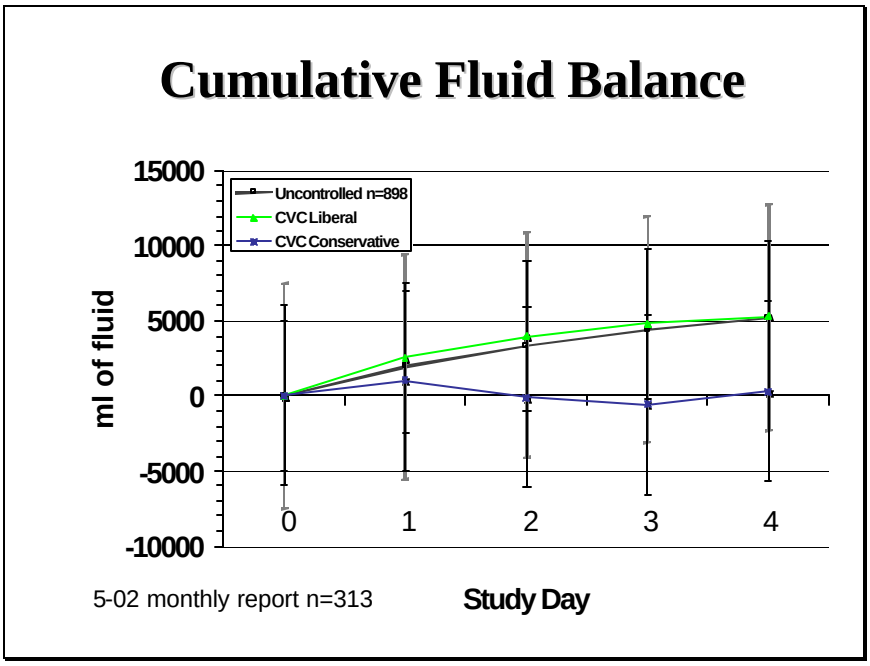

Figure 11: Cumulative fluid balance (ml; mean +/- standard deviation) for ARDSNet study 01 (ARMA; Uncontrolled) and the two CVC arms of FACTT.

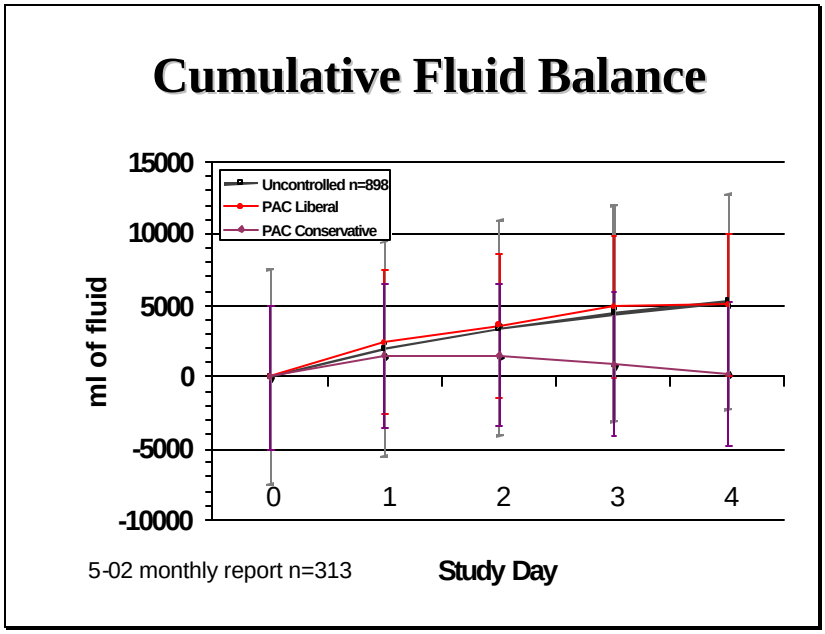

Figure 12: Cumulative fluid balance (ml; mean +/- standard deviation) for ARDSNet study 01 (ARMA; Uncontrolled) and the two PAC arms of FACTT.

(c) The FACTT protocol stated the following:

> ***"The second trial consists of randomization to either fluid 'liberal' or 'conservative' management strategy. Each of these strategies is thought to have potential benefit (such as lung protection in the 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."***

(d) Because of the apparent failures noted in (a) and (b) above, and the information cited in (c) above, the FACTT study appears to lack a control group appropriate for such a phase III clinical trial. Specifically, the study appears to lack a control group that receives either of the following:

(i) Individualized fluid management with target CVPs or PAOP's set at levels anywhere along the spectrum of these variables based upon consideration of a number of complex clinical factors unique to each subject, and the expertise, training and clinical judgment of a team of intensive care physicians (hereafter referred to as a "standard of care" fluid management control group); or

(ii) Protocol-mandated fluid management with target CVPs or PAOPs set either at target levels representing the means of the normal levels of CVP or PAOP, or at target

levels representing, as appropriate based upon systematic assessment of routine clinical practice, the mean, the median, mid-range, or mode of CVP and PAOP target levels sought in routine clinical practice at the time the study was conducted (hereafter referred to as an "average" fluid management control group).

As detailed in the responses to B. (1)(a) and B. (1)(b) above, the ARDSNet investigators maintain that he ARDSNet Study 05 (FACTT) protocol does provide individualized management of fluids and intravascular pressures based upon a number of clinical factors that are unique to a given patient (see the listing under "protocol safeguards"), and that the ARDSNet Study 05 (FACTT) protocol design was based upon the collective expertise, training, and clinical judgment of a team of intensive care physicians (the ARDSNet investigators). Furthermore, if in the opinion of the physicians taking care of the patient, an individualized, patient-specific protocol instruction deviates from safe and reasonable care for that specific patient, then the physician is allowed and encouraged to "override" the protocol (but asked to record the circumstances, so that the frequency and clinical context of such overrides can be analyzed). The frequency of such overrides in the first 404 patients is approximately 11% (see table 13 in the November 27th, 2002, FACTT monthly report in Appendix K.) In short, the ARDSNet Study 05 (FACTT) protocol does not force patients to be managed with fluid management or intravascular pressures that are contrary to the expertise, training, and clinical judgment of intensive care physicians. Figures 9-12 illustrate that the fluid management and intravascular filling pressures achieved during conduct of the ARDSNet Study 05 (FACTT) protocol are well within the wide range of routine clinical practice, and do not indicate that patients are being forced into rigid filling pressure ranges. For example, although the "target" PAOP in the "conservative" group is less than 8 mmHg, these patients actually have a PAOP of 13.4 +/- 5.8 mmHg on day 1 and 12.73 +/- 5.5 mmHg on day 2 of the trial – *pressures in the middle of the range of routine practice.*

(e) As a result of (a) – (d) above, it appears that after the completion of the FACTT study, there will be insufficient evidence to support any conclusion that either the liberal or conservative fluid management strategy is superior either of the following:

(i) Individualized "standard of care" fluid management; or

(ii) A fluid management strategy with target CVPs and PAOPs routinely set either at levels representing the means of the normal levels of CVP and PAOP, or at levels representing the mean, median, mid-range or mode of CVP and PAOP target levels sought in routine clinical practice.

As articulated in our responses above, the ARDSNet investigators maintain that there is no specific rationale for including an experimental arm that arbitrarily targets the means of the normal levels of CVP and PAOP, or levels representing the mean, median, mid-range or mode of CVP and PAOP of routine clinical practice, which is highly variable. We maintain that such a strategy is devoid of physiologic rationale, tests no specific hypothesis, provides little in the way of interpretable data, and would have no meaningful impact on clinical practice.

In contrast, the ARDSNet Study 05 (FACTT) protocol tests two specific hypothesis-driven management strategies that are well within the wide range of current routine clinical practice.

If one of these strategies were proven superior to the others, it would provide important information and insight to clinicians regarding the management of future patients.

(f) As a result of (a) – (d) above, both groups of experimental subjects in the FACTT study may be placed at an increased risk of death in comparison to patients managed according to a "standard of care" fluid management control group strategy or an "average" fluid management control group strategy because:

(i) The two experimental groups may be managed with target CVPs or PAOPs set at a level that may be lower or higher than either the means of normal CVPs and PAOPs or the target levels most commonly sought in routine clinical practice; and

(ii) the relationship of mortality to CVPs and PAOPs may be quadratic, resulting in a U- or J-shaped curve (the existence of a U-shaped curve was acknowledged by the ARDSNet investigators at the August 30, 2002 meeting convened by NHLBI).

As already illustrated in figures 9-12, and discussed in the related text, both experimental groups were managed with filling pressures that were near the middle of the range used in routine clinical practice. Furthermore, we do not perceive a scientific rationale for testing the "average" of the current widely variable practice, rather than comparing the two hypothesis-driven ARDSNet Study 05 (FACTT) strategies that are well within current routine practice boundaries. In fact, strict adherence to a target of "average" management would be unresponsive to concerns about appropriate individualization of management, based upon a patient's physiology. In contrast, the ARDSNet Study 05 (FACTT) protocols are highly responsive to individual patient physiology.

Although we acknowledge that the presence of a quadratic relationship between mortality and the range of CVPs and PAOPs utilized in routine clinical practice is theoretically possible, we regard it as only speculative and without any supporting published scientific data. Furthermore, the "separation" between the ARDSNet Study 05 (FACTT) treatment groups of net fluid balance and intravascular pressures is modest compared to the wide variability seen in routine practice. (See figures 9-12).

(g) As a result of (a)-(d) above, any increased risk of death for the two experimental groups of study subjects may go undetected because of the failure of the FACTT study design to include either a "standard of care" fluid management control group or an "average" fluid management control group.

An arm in which fluid management was entirely unregulated (routine clinical care) was considered, but rejected for reasons already discussed (see section B.1.b.)

As stated above, the ARDSNet investigators do not perceive a scientific rationale for testing the "average" of currently widely variable practice. Also, strict adherence to a target of "average" management would be unresponsive to concerns about appropriate individualization of management based upon a patient's physiology. In contrast, the ARDSNet STUDT 05 (FACTT) protocols are highly responsive to individual patient physiology. In this regard, it is important to note that a large number of the ARDSNet Study 05 (FACTT) patients randomized to the "liberal" strategy have a fluid balance *below* the

average, and a large number of the patients randomized to the "conservative" strategy have fluid balance *above* the average (as shown in figures 9-10).

It is critical to emphasize that the DSMB is able to compare the mortality observed in the experimental arms of ARDSNet Study 05 (FACTT) with the mortality observed in the earlier ARDSNet trials (e.g., ARDSNet Study 01 (ARMA), in which fluid management was entirely unregulated.

(h) In response to these previously presented concerns, the ARDSNet investigators have stated that there is no standard of care for patients with ALI and ARDS on mechanical ventilation with respect to fluid management strategy, and that target levels for CVP and PAOP selected for the two experimental groups are within the range used in routine clinical practice.

OHRP acknowledges that the target levels for CVP and PAOP used for the two experimental groups are within the range used in routine clinical practice at the time when the study was designed and initiated. However, as previously noted, "within the range used in routine clinical practice" and "routine clinical practice" are not equivalent concepts. Presumably, in routine clinical practice at the time the study was initiated, patients with ALI and ARDS were treated with fluid management strategies that allowed individualized target levels of CVP or PAOP selected from anywhere along the continuum for these variables based upon the expertise, training and clinical judgment of a team of intensive care unit physicians, taking into consideration a number of complex clinical factors unique to each subject. Presumably, such routine clinical practice did not result in assignment of patients to fluid management strategies under which target levels of CVP and PAOP are set at a high or low level based upon random choice.

Please respond in detail to each of the above items.

We agree that "within the range used in routine clinical practice" and "routine clinical practice" are not equivalent concepts. However, we do not agree with how OHRP interprets the broad range of fluid balance, CVP, and PAOP that are observed in routine practice. Whereas OHRP presumes that target levels of CVP or PAOP are selected "based upon the expertise, training, and clinical judgment of a team of intensive care unit physicians, taking into consideration a number of complex clinical factors unique to each subject", we maintain that there are no commonly accepted principles by which physicians select targets for fluid balance or intravascular pressures from within the wide range observed in routine care. Rather, we maintain that routine clinical care is <u>not</u> guided by evidence demonstrating how to utilize CVP and PAOP to improve outcomes of patients, and point out that clinicians offer a wide range of "target" PAOPs *without* reference to specific patient physiology [1]. We also re-emphasize that the ARDSNet Study 05 (FACTT) protocol provides a high degree of individualized management while testing specific hypothesis-based approaches, and does not request that a physician implement an instruction that would he or she would judge to be adverse for a particular patient, based upon that physician's expertise, training, and clinical judgment (see also discussion of "overrides" in section 10.l.).

(2) Please clarify whether or not, prior to designing the FACTT study, the ARDSNet investigators conducted a pre-study review and analysis of fluid management strategies used in routine clinical practice within the intensive care units of participating ARDSNet institutions in order to determine the range and frequency distribution of (a) the target

levels of CVPs and PAOPs set by intensive care unit physicians, and (b) the levels of CVPs and PAOPs actually attained during the treatment of the type of patient population eligible for the FACTT clinical study. In your response, please address the following, as appropriate:

(a) If such a pre-study review and analysis was conducted, please provide the complete results of that review and analysis.

As outlined in our response above to B.1.a, and as illustrated in Figure 9, the ARDSNet did have available to it, and did fully consider and explore, the net fluid balance of patients enrolled in the ARDSNet Study 01 (ARMA) trial, in which there was no protocol regulation of fluids or filling pressures. An analysis of these data revealed an extremely wide range of fluid balance, and the ARDSNet investigators were unable to identify an evidenced-based approach to account for this variability.

(b) If no such pre-study review and analysis was conducted, please clarify whether such a review and analysis was considered and explain the reasons for deciding not to perform such a review and analysis.

We did not carry out such a pre-study or analysis of CVPs and PAOPs actually measured at the ARDSNet centers in the treatment of the type of patients eligible for ARDSNet Study 05 (FACTT). The ARDSNet investigators recognized that there would be a large amount of missing data, since pulmonary artery catheters are utilized in only a minority of such patients, and that clinical practice regarding measurement and recording of both CVPs and PAOPs is highly variable. It is widely recognized that intravascular pressure measurements are subject to significant acquisition errors, in the absence of specific methodology to obtain valid and consistent measurements [62, 63]. Therefore, historical data obtained from the several ARDSNet intensive care units would be seriously flawed due to both missing data and a lack of standardized acquisition methodology. In contrast, the ARDSNet Study 05 (FACTT) protocol and manual of operations includes specific guidelines and instructions regarding the acquisition of intravascular pressure measurements and assurance of their quality.

(c) Please clarify whether the investigators or IRB at any participating institution requested such a pre-study review and analysis prior to approving the research. If so, please provide all correspondence and pertinent IRB records related to such a request.

To our knowledge, no IRBs at participating institutions requested information beyond that which is provided in the protocol documents.

(3) If no data are available with respect to the type of pre-study review and analysis described in item (2) above, please arrange for each site participating in the FACTT trial to conduct a review of the clinical records for a representative consecutive sample of patients who were diagnosed with ALI or ARDS, were managed with either a central venous catheter or a pulmonary artery catheter, and would have satisfied the study enrollment criteria immediately prior to initiation of enrollment of subjects at the site. Based upon this review, please provide the following:

(a) Number of patients reviewed for each site.

Will require site chart review.

(b) Dates on which ventilator therapy was initiated and catheter was placed for each patient.

Will require site chart review.

(c) A frequency distribution of the target levels of CVP and PAOP sought, and the actual CVP and PAOP levels measured, on days 1 thru 7 of catheter management for each ARDSNet study site and for all sites combined.

It may not possible to provide the requested data on consecutive samples of patients with ALI or ARDS at all of the ARDS Network hospitals because not all hospitals keep logs of such patients. We are working on potential strategies to identify such patients with sites.

(4) Please explain the basis for selecting the two experimental groups (low target levels of CVP or PAOP or high target levels of CVP or PAOP). Was there any pre-study basis to assume that these two fluid management strategies would be safer and more effective than either a "standard of care" fluid management control group strategy or an "average" fluid management control group strategy? Were the fluid management strategies for the two experimental groups selected based upon the expectation that this would increase likelihood of showing statistically significant difference between the two experimental groups?

The current concept regarding fluid management in ALI/ARDS patients is that a lower vascular filling pressure/volume status prioritizes the lungs (reduced pulmonary edema, improved compliance, better gas exchange), whereas a higher vascular filling pressure/volume status prioritizes cardiac output and organ perfusion (improved kidney function, etc). However, there is very little evidence to guide physicians in how to reconcile these priorities in a given patient, and we believe this accounts for much of the wide variability of routine practice. The experimental groups of ARDSNet Study 05 (FACTT) were designed to provide a "conservative " fluid strategy and a "liberal" fluid strategy that were each well within the wide range of routine care and responsive to individual patient physiology. Patients are not forced into rigid target ranges.

We believe that several features of ARDSNet Study 05 (FACTT) probably enhance the safety of enrolled patients, relative to routine care. For example, the protocol and manual of operations contain specific guidelines regarding the accurate acquisition and measurement of intravascular filling pressures (CVP and PAOP). In addition, study personnel at each site receive training regarding these guidelines, and compliance is monitored throughout the trial by a system of random daily checks and external review. As the result of these processes, patients enrolled in ARDSNet Study 05 (FACTT) are protected against errors of acquisition and measurement of intravascular pressures, which are identified as a significant problem in routine care [62-64] Furthermore, as detailed in B.1.b, patients enrolled in ARDSNet Study 05 (FACTT) benefit from a number of protocol safeguards, including a detailed assessment of their cardiopulmonary and renal status at least every four hours, and protocol instructions that take into account very individualized aspects of their physiology, such as their own prior responses to fluid boluses and diuretic administration. In addition, the patient's treating physician is encouraged to "override" protocol instructions that he or she views as inappropriate or unsafe, which occurs about 11 % of the time (see section 10. l.). Taking all of the above mentioned considerations into account, we believe there is no basis to conclude that routine care is safer to patients than is enrollment in ARDSNet Study 05 (FACTT).

We believe that an "average" fluid management is devoid of physiologic rationale, and, in any event, difficult to define and operationalize. For example, based upon the ARDSNet Study 01 (ARMA) fluid balance data, the "average" management strategy would achieve a positive net fluid balance of about 1000 cc per day. If this were the target for one arm of ARDSNet Study 05 (FACTT), it would be impossible to reach this goal and still preserve individualized, patient-specific therapy. In contrast, the ARDSNet Study 05 (FACTT) protocol does provide individualized instructions based both upon a patient's current physiology and pattern of response to previous protocol instructions. It is particularly relevant to point out that a large number of the ARDSNet Study 05 (FACTT) patients randomized to the "*liberal*" strategy have a fluid balance *below* the average, and a large number of ARDSNet Study 05 (FACTT) patients randomized to the "conservative" strategy have a fluid balance *above* the average. (See figures 11 and 12). Similarly, suppose a PAOP of 10 mmHg was identified as the average therapy (based on Carmichael, et al [1]). It is noteworthy that many ARDSNet Study 05 (FACTT) "conservative" management patients have PAOP values *above* 10 mmHg, and many patients randomized to the "liberal" strategy have a PAOP *below* 10 mmHg. (See figures 9 and 10). These observations provide critical insight into ARDSNet Study 05 (FACTT). In particular: 1) ARDSNet Study 05 (FACTT) is designed to test two specific strategies that are each highly responsive to individual patient data and history of physiologic responses, and 2) ARDSNet Study 05 (FACTT) is not designed to force a separation into two distinct and non-overlapping management strategies with one always being above the "average" and the other always below the "average".

Quite definitely, therefore, the management strategies were not selected with the aim of increasing the likelihood of showing a statistically significant difference between the two experimental groups. Rather, we aimed to determine whether there would be a difference in outcome when two explicit and reasonable management strategies, both within the range of routine practice and responsive to underlying patient physiology, were compared. If no difference in outcome is found, we would still view this an important contribution to clinical practice.

(5) Did the ARDSNet investigators take into account any animal studies assessing the mortality rate of animals assigned to multiple different target levels of CVP or PAOP over a wide range of each of these variables? Is so, please provide relevant literature. If not, did the ARDSNet investigators consider conducting such animal studies before initiating this clinical trial in humans?

We are unaware of an animal model of acute lung injury that duplicates the multi-system pathophysiology and natural history of ALI/ARDS in humans. A recent study compared four widely used animal models of acute lung injury to determine the acute changes in physiologic variables associated with each model in pigs [67]. Two of the models, bronchoalveolar instillation of hydrochloric acid and repeated bronchoalveolar saline lavage, resulted in significant hypoxemia, but no change in pulmonary vascular resistance or cardiac output. Spontaneous improvement in gas exchange was noted in both models over time. In contrast, endotoxin infusion did not result in hypoxemia but caused significant increases in mean pulmonary artery pressure and pulmonary vascular resistance, and decreases in mean arterial pressure and cardiac output. Intrapulmonary arterial infusion of oleic acid resulted in marked hypoxemia with a profound increase in mean arterial pressure

and pulmonary vascular resistance, as well as a marked reduction in mean arterial pressure, cardiac output, and mixed venous PO_2. None of these patterns of response match the acute respiratory and hemodynamic characteristics of patients with ALI/ARDS enrolled in the ARDSNet trials. For example, the patients enrolled in ARDSNet Study 05 (FACTT) exhibit a significantly elevated cardiac index of 4.65 +/- 0.30 [68].

In addition to the fact that animal models are limited in their ability to duplicate the full range of respiratory and systemic pathophysiology that exists acutely in ALI/ARDS patients, we are unaware of any animal model that is sustained for several days and displays the gradual progressive organ dysfunction and mortality that occurs in many patients.

There are no animal studies of acute lung injury that assess the mortality rate of animals assigned to multiple different targets of CVP and PAOP over a wide range of these variables. However, several animal studies suggest that intravascular filling pressures and volume status influence lung physiology. In the treatment of canine aspiration pneumonitis, intravascular fluid balance influences PAOP and pulmonary edema [69]. Short-term animal models also demonstrate that furosemide and ultrafiltration are able to lower both PAOP and extravascular lung water [70, 71] Other studies indicate that furosemide reduces pulmonary edema and enhances gas exchange, but that these effects could not be attributed to either decreased PAOP or increased colloid osmotic pressure [72, 73]. Putative "non-diuretic" actions of furosemide include effects on ventilation – perfusion matching or the permeability co-efficient of the pulmonary capillary endothelium [73].

Overall, the ARDSNet investigators believe that currently available animal models of acute lung injury provide a firm foundation for the concept that a lower vascular filling pressure/volume status, achieved in part by the use of furosemide, prioritizes the lungs (reduced pulmonary edema and better gas exchange) in patients with ALI/ARDS. However, we do not feel that there are available and appropriate animal models to test the application of our comprehensive fluid management strategies over several days.

(6) Please provide evidence from any human studies that supports the conclusion that the two fluid management strategies selected for the trial are safer or more effective than either a "standard of care" fluid management control group strategy or an "average" fluid management control group strategy. In providing your response, please note that the IRB –approved FACTT protocol provides a theoretical basis for why each of the experimental fluid management strategies selected for the FACTT trial may be less advantageous than a fluid management strategy that is either individualized or attempts to maintain a level of CVP or PAOP in the middle of the normal range.

The specific ARDSNet Study 05 (FACTT) management strategies, although designed by expert clinicians and approved by an independent PRC and DSMB, had not been previously tested. We did disclose this in the protocol and informed consent documents, and initiated ARDSNet Study 05 (FACTT) with a phase II investigation.

As discussed under B4, the ARDSNet Study 05 (FACTT) management strategies are more flexible and individualized than one which would attempt to maintain a level of CVP or PAOP in the middle of the normal range (or middle of the wide range utilized in ARDS

patients, as well). We do not perceive an *a priori* theoretical or evidence-based reason to assume that the ARDSNet Study 05 (FACTT) strategies would be less advantageous or less safe than an attempt to maintain patients at middle or average values. In fact, an attempt to maintain patients at a middle or average value would result in less flexibility and responsiveness to patient –specific physiology than do the ARDSNet Study 05 (FACTT) protocols. As previously noted (section B.4.), both the "liberal" and the "conservative" groups have patients who are managed above and below the average values for fluid balance and intravascular filling pressures. ARDSNet Study 05 (FACTT) does not separate the treatment groups into non-overlapping interventions, in which all the patients in one group are managed below an average value and all patients in the other group are managed above an average value.

As previously discussed (Section 4.), we believe that several features of ARDSNet Study 05 (FACTT) probably enhance the safety of enrolled patients, relative to routine care. For example, the protocol and manual of operations contain specific guidelines regarding the accurate acquisition and measurement of intravascular filling pressures (CVP and PAOP). In addition, study personnel at each site receive training regarding these guidelines, and compliance is monitored throughout the trial by a system of random daily checks and external review. As the result of these processes, patients enrolled in ARDSNet Study 05 (FACTT) are protected against errors of acquisition and measurement of intravascular pressures, which are identified as a significant problem in routine care [62-64]. Furthermore, as detailed in B.1.b, patients enrolled in ARDSNet Study 05 (FACTT) benefit from a number of protocol safeguards, including a detailed assessment of their cardiopulmonary and renal status at least every four hours, and protocol instructions that take into account very individualized aspects of their physiology, such as their own prior responses to fluid boluses and diuretic administration. In addition, the patient's treating physician is encouraged to "override" protocol instructions that he or she views as inappropriate or unsafe, which occurs about 11 % of the time (see section 10. l.). Taking all of the above mentioned considerations into account, we believe there is no basis to conclude that routine care is safer to patients than is enrollment in ARDSNet Study 05 (FACTT).

(7) OHRP is concerned that the BACKGROUND section of the FACTT protocol provides little, in any, substantive discussion explaining the basis for selecting the two experimental fluid management strategies that were to be used. As a result, it is unclear how any of the reviewing IRBs could have made the determinations required for approval under 45 CFR 46.111(a)(1) and (2). Please respond in detail. In your response, please clarify whether any IRB from the participating ARDSNet institutions requested additional information from the ARDSNet investigators regarding the basis of the study design with respect to the inclusion of only two experimental fluid management groups and the exclusion of any "standard of care" fluid management control group or "average" fluid management control group. If so, please provide all correspondence and pertinent IRB records related to such a request.

The BACKGROUND section of the ARDSNet Study 05 (FACTT) protocol does discuss and reference the two human studies (61,62) that provide some limited support for the concept that lower vascular filling pressures and fluid balance in ARDS patients is associated with improved clinical outcomes, and cites animal data indicating that high pulmonary capillary pressures may lead to ultrastructural damage and inflammation. Also

cited is a review article that reviews the issues and controversies regarding fluid and hemodynamic management in acute lung injury. Therefore, we believe that the BACKGROUND section provides a foundation for understanding the ARDSNet Study 05 (FACTT) experimental fluid management strategies, even though the development and design of these strategies is not discussed in the BACKGROUND section. The ASSESSMENT OF RISKS section does refer to the two management strategies, their design by expert consensus, and their overall rationale. Appendix I provides the complete and explicit protocol for all of the management strategies. Overall, we believe that the required elements are present in the protocol; however, a more thorough discussion of the rationale behind the specific elements of the experimental strategies and how the strategies would operate in specific clinical circumstances would have been reasonable to include.

We are not aware of any IRB that requested additional information from the ARDSNet investigators regarding any elements of the study design.

(8) OHRP notes that the FACTT protocol stipulates that all subjects are to be placed on low tidal volume protocol (6 ml/kg PBW). As noted in section A, there appears to be insufficient evidence to support the conclusion that this tidal volume is superior to routine clinical practice or to tidal volumes in the range of 7-11 ml/kg PBW. Indeed, at the August 30, 2002 meeting convened by NHLBI, the ARDSNet investigators appeared to acknowledge that the ARMA trial was not designed to determine the "best tidal volume" overall, only whether 6 ml/kg or 12 ml/kg PBW is better. As a result, this protocol-mandated tidal volume intervention may compound the risks associated with the experimental fluid management strategies and result in a failure to minimize risks to subjects, as required by HHS regulations at 45 CFR 46.111(a)(1). Please respond in detail. In providing your response, please note that the IRB-approved ARMA protocol provided a theoretical basis for why tidal volumes of 6 ml/kg may pose greater risk of harm and discomfort in comparison to the use of higher tidal volumes that are less than 12 ml/kg PBW, but limit the level of plateau airway pressure. These include an increased probability of developing hypercapnia, respiratory acidosis (requiring more sodium bicarbonate), volume overload, hypernatremia, agitation and dyspnea (requiring greater sedation), and oxidant-induced lung injury secondary to higher FiO_2 requirements.

ARDSNet investigators reiterate that ARDSNet Study 01 was not designed specifically to determine the best tidal volume overall. However, since conclusion of the trial, statistical analyses of the study database strongly suggest that *tidal volumes of 6 ml/kg PBW are safer than routine clinical practice or to tidal volumes of 7-11 ml/kg PBW*. These analyses are reviewed in our previous responses to issue A.(7).

For issue A.(9), OHRP requested data on patients who were excluded from ARDSNet Study 01. These patients would have received ventilator management according to routine care practices. Mortality was substantially higher in these patients than in those enrolled in ARDSNet Study 01 [74].

Patients who refused to participate (eligible nonparticipants, ENPs) are a potentially useful comparison group in this context because they met all of the inclusion criteria, none of the exclusion criteria (except that they declined to participate), and they were cared for contemporaneously in the same hospitals as the patients who participated. Institutional review

boards for most hospitals allowed ARDS Network investigators to use data on ENPs. There were 260 ENPs and 668 participants at these hospitals. There were imbalances in some of the characteristics that predict mortality between ENPs and participants. For example, PaO_2/FiO_2 ratios on the day of enrollment (or potential enrollment) were higher in the ENPs than the participants (146 vs. 134, p = 0.01. Lower PaO_2/FiO_2 is a predictor of mortality.). After adjustments for the imbalances between the groups, the odds ratio for mortality of the lower tidal volume study group compared to ENPs was 0.92 (p = 0.64).

Mortality before hospital discharge in the lower tidal volume group of ARDS Network Study #01 (n = 432) was 31%. In a subsequent ARDSNet study in which lower tidal volumes were used in all patients (n = 550), mortality before hospital discharge was 26% [75]. These mortality rates are low compared to those reported in other large groups of ALI patients in which lower tidal volume ventilation was not used. For these reasons, we consider the ARDSNet Study 01 lower tidal volume protocol to be a good standard for mechanical ventilation in ALI/ARDS.

Many investigators independent of ARDSNet have recommended that the ARDSNet Study 01 lower tidal volume protocol should be considered a "standard".

1. In his editorial to the Eichacker article, Thomas E. Stewart, M.D. wrote, "I believe it [ARDSNet's lower tidal volume protocol] is the intervention against which future ventilator strategies should be tested"[76].

2. In his editorial to the Eichacker article, Richard Albert, M.D. wrote, "In the two years since its publication, low tidal volume ventilation has become the international standard for ventilatory support of patients with ALI/ARDS." (Web MD: Respiratory and Critical Care; http://webmd.com).

3. In an editorial to a recently published paper regarding education of medical residents, William F. Dunn referred to the ARDS Network lower tidal volume protocol as a "literature established best-practice norm." [77]

4. In the recently published trial of high frequency oscillatory ventilation in ALI/ARDS, the investigators said, "…HFOV should be compared with the current 'gold-standard' CV strategy such as the low tidal volume strategy used in the ARDS Network trial"[78].

5. In a recent study of molecular pathogenesis of ventilator associated lung injury [79], the authors stated, "This sentinel study [ARDSNet Study 01] has changed the routine care for ventilator management of patients with ALI/ARDS."

6. In a letter to the editor of the American Journal of Respiratory and Critical Care Medicine, Thomas L. Petty, M.D., a senior clinical scholar considered by many to be the "father" of ALI/ARDS research, said, "Their [ARDSNet's] study now provides a sound scientific basis for the present routine care." (Appendix I)

7. According to the soon-to-be-published American-European Consensus Conference III on ARDS, "the recommendation is to decrease tidal volume initially to ~6 ml/kg lean body weight. Assess plateau pressure and consider further reductions in tidal volume if necessary to achieve a plateau pressure below 30 cm H_2O."

8. In an on-going trial of lower versus higher PEEP conducted by the Canadian Critical Care Clinical Trials Group, the "control group" uses the ARDSNet lower tidal volume protocol (Thomas Stewart, personal communication).

9. The control group in an on-going French trial of higher PEEP also uses a target tidal volume of 6 ml/kg PBW and inspiratory plateau pressure limit of 30 cm H_2O (Laurent Brochard, personal communication).

10. According to the study protocol for the recently completed Byk-Gulden/Altana trial of Venticute (surfactant) in ARDS, "Application of the ARDSNet 6 ml/kg Tidal Volume Strategy … should be used during all periods of the study."

11. The protocol for the recently completed Eli Lilly trial of a neutrophil elastase inhibitor in ARDS also included the ARDSNet lower tidal volume protocol.

12. The following statement is from a chapter entitled "New Mechanical Ventilation Strategies" in Harrison's Online: "Based on the ARDSNet results, … a target Pplat < 30 cm H_2O should be used in patients with ALI and ARDS. The ARDSNet protocol is shown in Table 1." [80]

13. The following recommendation for tidal volume and plateau pressure limit is included in "Acute Lung Injury and Acute Respiratory Distress Syndrome", a chapter in Essentials of Mechanical Ventilation, McGraw-Hill, 2nd edition, 2003: "The target tidal volume is 6 ml/kg and is maintained between 4 and 8 ml/kg. Tidal volume is set based upon predicted body weight….The target plateau pressure is 25-30 cm H_2O." Table 13-5 of this chapter includes a comprehensive summary of the lower tidal volume protocol procedures.

14. In the 423 ALI/ARDS patients who have been enrolled in ARDSNet Study #05, the most commonly used (mode) tidal volume prescribed by physicians before randomization was 6 ml/kg PBW, and 60% of all tidal volumes were $\leq$ 7.5 ml/kg PBW.

(9)Please provide a complete list of all ARDSNet institutions participating in the FACTT trial. Please include the following for each site: local principal investigator name, date of initial IRB approval, date first subject was enrolled, and number of subjects enrolled to date.

See file `factt_site-structure\site_structure.xls` on the included CD.

(10) For each individual subject for whom informed consent was obtained and documented, please provide the following information in tabular or spreadsheet format:

Requested data elements that are available in the ARDSNet CCC database have been provided on the included CD in tab delimited .txt files suitable for import into Excel or other

spreadsheet or database applications. The baseline and outcome data requested in items (a), (f), (i), (j), and (m) is included in the file
`factt\data\ohrp_factt_baseline_outcome.txt.`

The on study data requested in item (k) is included in the file
`factt\data\ohrp_factt_on_study.txt`.

The fluid management protocol override data requested in item (l) is included in the file
`factt\data\ohrp_factt_protocol_override.txt`.

The PAC and CVC complications data requested in item (m) is included in the file
`factt\data\ohrp_factt_pac_cvc_complications.txt`.

An additional file, `factt\data\ohrp_factt_data_dictionary.txt`, is a data dictionary which fully describes the structure of each of the tab delimited data files. Simple summary statistics for all data elements are provided in confidential Appendix J.

(a) Site of enrollment.

See file `factt\data\ohrp_factt_baseline_outcome.txt`

(b) Date informed consent was obtained and documented.

See file `factt\ic_withdrawal\factt_ic.xls`

(c) If a surrogate signed the informed consent document, the relationship of the surrogate individual to the subject.

See file `factt\ic_withdrawal\factt_ic.xls`

(d) Number of consecutive days on mechanical ventilation prior to enrollment in the clinical trial.

Pending chart review at sites.

(e) Number of consecutive days with CVC in place prior to enrollment in the clinical trial.

Pending chart review at sites.

(f) Predicted (or ideal) body weight.

See file `factt\data\ohrp_factt_baseline_outcome.txt`

(g) For each day the subject was on mechanical ventilation prior to randomization, up to a total of 7 consecutive days moving back in time, please provide the mode of mechanical ventilation, the tidal volumes used, and plateau pressures measured.

Pending chart review at sites.

(h) If the subject had a CVC in place prior to randomization, please provide the CVP measurements that were recorded for each day the CVC was in place for up to 7 consecutive days prior to randomization.

Pending chart review at sites.

(i) If the subject was not randomized, an explanation as to why randomization did not occur. For each randomized subject, identify the experimental group to which the subject was assigned.

All subjects who gave informed consent were subsequently randomized .

(j) The following baseline data: age, gender, systemic systolic and diastolic blood pressure, heart rate, APAHCE III score, tidal volume, plateau airway pressure, peak inspiratory pressure, FiO_2, PaO_2, pCO_2, arterial pH, CVP, PAOP, serum electrolytes, BUN, creatinine, hematocrit/hemoglobin, urinary output (most recent 24-hour value), and intake and output for 24 hours.

See file `factt\data\ohrp_factt_baseline_outcome.txt`

(k) The following data for days 1 to 7 post randomization: systemic systolic and diastolic blood pressure, heart rate, tidal volume, plateau airway pressure, peak inspiratory pressure, FiO_2, PaO_2, pCO_2, arterial pH, CVP, PAOP, serum electrolytes, BUN, creatinine, hematocrit/hemoglobin, 24-hour urine and other output, total volume input, total dose of Lasix administered, vasopressor administration (type and dose), and inotropic agent administration (type and dose).

See file `factt\data\ohrp_factt_on_study.txt`

(l) Data regarding number of times the protocol-mandated fluid management strategy was overridden by the primary healthcare provider and reasons for each override.

See file `factt\data\ohrp_factt_Protocol Overrides.xls`

This file contains the reasons for physician overrides in the first 66 subjects enrolled in FACTT. See also Tables 12 and 13 of the November 27th, 2002 FACTT monthly report reviewed by the DSMB on December 13th that is included in Appendix K. These tables list the percentage of all instructions declined by treatment assignment for the initial, ~84 patient, Phase II protocol validation portion of FACTT and for a random daily sample of instructions accepted or declined since this early phase.

During the protocol validation portion of the trial, ~ weekly conference calls with the FACTT Executive Committee and investigators were conducted. All instructions were reviewed on the call (n=2225) and reasons for declining instructions discussed (n=182). The findings for the first 66 patients were summarized in the June 11, 2001 FACTT Executive Committee refinement analysis. This report along with a detailed statistical analysis of the first 84 patients by the CCC was reviewed by the DSMB in June 18, 2001. The DSMB recommended that the study continue. Excerpts from this report related to physician overrides follows in 11 point font, indented:

> **Excerpts from the June 11, 2001 Phase II Refinement analysis:**
>
> **5.4.2 Instruction Refusals / Overrides**
>
> There were 182 occasions where the protocol was deliberately not followed henceforth called "overrides". The median number of overrides per patient was 0, the mean number was 2.8+/-4.8. Overrides were most common among patients randomized to PAC conservative n=95 (14.5% of all instructions for that group). CVC conservative patients had the next highest number of overrides 35 (6.5%) followed by CVC liberal 31 (4.9%) and PAC liberal 21 (5.1%). Of note, six patients accounted for 51% of the protocol overrides and four of these six patients were randomized to PAC conservative.
>
> **5.4.2.1 Furosemide Overrides**

The most common instruction refused was administration of any, or the protocol indicated, dose of furosemide (n=120): on 43 occasions because of an unacceptable BUN or creatinine; on 32 occasions because of unacceptable sodium or potassium; on 22 occasions for no recorded reason; and on 10 occasions for some reason to do with "contrast media". On 13 occasions furosemide was administered when indicated but the protocol mandated dose was not used (Both larger and smaller than protocol indicated doses were given). On 16 occasions furosemide was given without a protocol instruction. Nine of these episodes occurred while patients were in shock.

5.4.2.2 Fluid Bolus Overrides

Fluid boluses were refused or altered in size on 27 occasions. On 17 of these occasions a fluid bolus was refused in cell #19 for unknown reasons or because the urine output was judged to be "adequate" or "high".

5.4.2.3 Dobutamine Overrides

Dobutamine was refused on 6 occasions all because "cardiac index was adequate"

(m) Data with respect to the following outcomes variables: mortality prior to hospital discharge to day 60 (if death occurred, please indicate the number of days post randomization when death occurred), number of ventilator free days to 28 days after enrollment, number of ICU-free days at 7 and 28 days after enrollment, and number and type of complications associated with PAC and CVC while catheters were in place.

See files `factt\data\ohrp_factt_baseline_outcome.txt` and `factt\data\ohrp_factt_pac_cvc_complications.txt`

(n) With respect to outcome variables, please include whether any subject was withdrawn from the study, the date of withdrawal, and reason for withdrawal (including withdrawal of consent by the subject or the subject's legally authorized representative, withdrawal by treating physician, protocol violation, or other reason). Please specify how subjects who withdrew from the study after randomization are being handled in the data analysis.

These subjects will be included in the data analysis. We will adhere to the "intent to treat" principle. See file `factt\ic_withdrawal\factt_wthdrw.xls`

(11) Please clarify whether the participating ARDSNet sites for the FACTT trial collected clinical and outcome data on any patients who were screened for participation in the clinical trial, but were not enrolled either because they refused participation or met exclusion criteria. If so, please provide a complete summary of all data collected on all such patients.

The data collected for the screened but un-enrolled patients is included in the tab delimited file `factt\data\ohrp_factt_screen.txt`. The structure of this file is also found in the data dictionary `factt\data\ohrp_factt_data_dictionary.txt` and summary statistics are included in confidential Appendix J. In addition the data entry screen for this form with the field names written in is included in Appendix L.

(12) Please provide a copy of all publications, abstracts, and manuscripts related to the FACTT trial.

Please see Appendix M.

(13) Please provide the statistical plan for the interim analyses and the outcome of each interim analysis by DSMB. Please include the following for each interim analysis:

DSMB meetings will be scheduled when 200, 400, 600, and 800 patients have been treated. A two sided O'Brien-Fleming boundary [81] 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. The test will be based on the Kaplan Meier estimate of 60 day mortality.

At each DSMB meeting a test for interaction will be performed. This test will be controlled for multiple comparisons using a Pocock boundary [82] 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 several 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. Please see part 2 of the ARDSNet DSMB report, Appendix K.

(a) Date of the DSMB review.

(b) Number of Subjects enrolled at the time of the review

(c) Summary data for each review including number of subjects enrolled in each experimental group; endpoints reached for each of the primary and secondary endpoints noted in (10)(m) above; and statistical tests used and p values for the comparison of each endpoint measurement between the two experimental groups.

TABLE 2 OMITTED

Table 2: Dates, actual and effective sample sizes, mortality (+/-SEM), and actual vs. protocol specified P values for stopping are given for each DSMB review of ARDSNet Study 05 (FACTT). Median ventilator free and organ failure free days are also given for each DSMB review. **CONFIDENTIAL**: This table appears only in reports sent to the OHRP and the NHLBI.

(14) OHRP is concerned that the FACCT (sic) protocol provides little substantive discussion of the multiple complex ethical issues related to human subject protections that are presented by such research. For instance, the protocol does not describe, among other things, the following:

(a) the justification for an informed consent process that involves surrogate consent for research involving greater than minimal risk and presenting possibly limited benefits to the subjects.

In contrast to the existence of special regulations involving children, the federal regulations do not provide a hierarchy of research categories establishing more rigorous substantive and procedural standards for proposals presenting more than minimal risk to decisionally incapable subjects. However, the general view for adults is that it is permissible to include incapable subjects in potentially beneficial research projects as long as the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting[50]. This standard is similar to the general demand for clinical equipoise when human subjects participate in clinical trials[51]. Several U.S. task forces have deemed it is permissible to include incapable subjects in greater than minimal risk research as long as there are the potential for beneficial effects. 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."[52] The Maryland draft legislation deems "expected medical benefit" research permissible if an agent or surrogate, "after taking into account treatment alternatives outside of the research, …concludes that participation is in the individual's medical best interest."[53] 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…"[54]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research, we believe that the ARDSNet Study 05 (FACTT) trial presented a balance of risks and expected direct benefits that is *similar* to that available in the clinical setting. As such, we disagree with OHRP's interpretation that the ARDSNet Study 05 (FACTT) trial involved greater than minimal risk and presenting "possibly limited benefits" to the subjects. Essentially, OHRP's interpretation is that the balance of risks and benefits in the ARDSNet Study 05 (FACTT) trial was greater than that available in the clinical setting.

The existing federal research regulations (45CFR46) acknowledge the possibility of proxy consent through the use of legally authorized representative (LARs)[55]. According to

NBAC, an investigator should accept as an LAR…a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place[54]. 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 [56].

(b) additional safeguards that were included for subjects who were likely to be vulnerable to coercion or undue (e.g., independent consent monitors);

The ARDSNet Study 05 (FACTT) research will most likely involve subjects who might be vulnerable to coercion or undue influence. Although not stated in the protocol, as required in 45CFR46.111(b), additional safeguards as specified by individual IRBs will be included to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) decision making standards for the basis of a LAR's decision; b) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; c) augmented consent processes; and d) independent monitoring of the subject's participation in the study, e.g., to ensure that the risk-expected benefit ratios continue to be acceptable throughout the course of the study. The specific nature of the additional safeguards should be left to the discretion of the individual IRBs.

(c) for subjects for whom consent would be initially obtained from a family member, a description of the procedure that would be followed for obtaining and documenting informed consent from those subjects who subsequently became capable of consent for themselves during the course of the trial;

The ARDSNet had previously surveyed its member sites on whether there was a process in place for obtaining informed consent from subjects who were initially enrolled via surrogate consent and subsequently became capable of providing consent for themselves during the course of the trial.

Results of this survey with a corresponding narrative are shown in Appendix N. Briefly, this survey demonstrated that all sites had a process in place for obtaining this type of consent. Subsequently, the DSMB recommended that all sites obtain formal consent from survivors for ongoing participation and that the initial consent form signed by the surrogate should reflect that such consent will be obtained (See confidential Appendix K).

(d) whether the research satisfies the requirements under HHS regulations at 45 CFR Part 46, Subpart D, for research involving children;

Research involving children is permissible under HHS regulations at 45 CFR Part 46.405, Subpart D, provided that the IRB finds that:

i) the risk is justified by the anticipated benefit to the subjects;
ii) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
iii) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

The ARDSNet Study 05 (FACTT) research study represents greater than minimal risk research with the prospect of direct benefits to subjects. We believe that the risks of the

ARDSNet Study 05 (FACTT) trial is justified by the anticipated benefit to the subjects and the relation of the anticipated benefit to the risks is at least as favorable to the subjects as that presented by available alternative approaches. Having said this, each participating IRB needs to make its own individual determination regarding this assessment of risks and benefits as well as whether adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

(e) the basis for excluding pregnant women.

The rationale for excluding pregnant women was due to the potential concerns with impaired perfusion to the uterus that might occur with randomization of such individuals to the fluid restrictive strategy. A further concern was with the effects of dobutamine in pregnant women, as the protocol instructs the use of this agent in certain situations. According to the American Hospital Formulary Drug Information, "Safe use of dobutamine during pregnancy has not been established. Dobutamine should be used in pregnant women only if clearly indicated." The PDR lists dobutamine as a category B drug for pregnancy.

(15) OHRP notes that the inclusion criteria in the FACTT protocol allow for subjects as young as 13 years to be enrolled in the trial. OHRP is concerned that the research may not satisfy the requirements of HHS regulations at 45 CFR Part46, Subpart D, for research involving children. Please clarify whether each IRB that approved the research approved the involvement of children. For each institution where the IRB approved the research for children, please indicate under which of the three categories of research described at 45 CFR 46.404-406 the research was approved and the justification for the category selected.

IRB responses on this issue are being obtained from the individual IRBs.

(16) Regarding the sample informed consent document (copy enclosed), OHRP has the following concerns and questions:

(a) In the section, INVITATION TO PARTICIPATE IN A RESEARCH Study, the last sentence states, "If you do not understand anything in this form, then your legal agent will be asked to make a decision for you."

(i) Please clarify the number of participating ARDSNet institutions that retain this language in their final IRB-approved informed consent documents.

(ii) Please clarify the intended meaning of "your legal agent."

(iii) Please describe the procedure for assessing subject understanding of each part of the informed consent document.

(iv) The statement appears to suggest that a subject could understand the most important information in the informed consent document and decide not to participate, but because of some perceived failure of the subject to understand even one minor element in the document, informed consent would be sought from another individual on behalf of the subject. Please explain the rationale for such an approach.

The sample consent form given to OHRP was sent to the ARDSNet on February 8, 2000 for review and hence, was not the final copy developed by the ARDSNet Ethics Committee. The final copy, included in Appendix O, was distributed to the ARDSNet on April 11, 2000. This copy does not have the language that is questioned by the OHRP. Our review of IRB approved consent forms for ARDSNet Study 05 (FACTT) indicates that none

contain this language (See Appendix P). Hence, the concerns expressed by OHRP in (16) are no longer relevant.

(b) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, the following information, among other things shall be provided to the subject or the subject's legally authorized representative: an explanation of the purpose of the research and a description of the procedures to be followed, and identification of any procedures which are experimental.

> ***(i) OHRP is concerned that the sample informed consent document fails to adequately describe the purpose of the research. Instead of stating that the purpose of the study is to compare the effectiveness of two different catheters and two different ways of managing fluids, it appears that it would have been more appropriate to state that the main purpose of the study was to find out if patients with ALI/ARDS have a higher or lower death rate when managed with a central venous catheter versus a pulmonary artery catheter and with a high fluid management strategy versus a low fluid management strategy. Please respond.***

The ARDSNet Study 05 (FACTT) study had several objectives: the primary objective was to compare the safety and efficacy of "PAC vs. CVC management" and "fluid liberal" vs. "fluid conservative" management in reducing *mortality* and *morbidity* in patients with acute lung injury. Accordingly, the primary efficacy variable was mortality, while major secondary efficacy variables included a) ventilator free days and b) organ-failure free days. Because there were several objectives of the study, involving mortality *and* morbidity, the "broad" phrase "to compare the effectiveness" was used. To be sure, we agree that giving potential subjects specific information on the "main purpose" of the study is warranted. We respectfully disagree, however, with the language suggested by OHRP, because a) it only states one of the primary objectives of the study and b) use of the passive voice does not state explicitly the link between the use of catheter and fluid management strategies and their potential effects on mortality.

Accordingly, we prefer to use language that is similar to what is stated in the protocol. Specifically, the informed consent should state: "This research study compares the effects of two different types of catheters when used in combination with one of two different fluid management strategies. These catheters are a central venous catheter and a pulmonary artery catheter. The purpose of this study is to determine whether there is a difference between different combinations of these catheters and fluid management strategies in reducing the death rate, reducing the time spent on the ventilator, and in reducing damage to your organs."

> ***(ii) OHRP is concerned that the sample informed consent document fails to adequately describe the nature of the experimental design and the differences between the experimental fluid management interventions and standard fluid management (which is listed as the alternative to participation). Furthermore, OHRP is concerned that the following statement in the PURPOSE OF THE Study section is inaccurate and conflicts with statements made in the FACCT protocol (see item B.1.c above)):"Both types of [fluid management] methods are considered standard of care." Please respond.***

The revised consent form contains the following paragraph in the PURPOSES OF THE Study section:

"The other purpose of this study is to compare the safety and effectiveness of two different ways of managing the amount of fluids in your body. One way minimizes the amount of fluids (fluid conservative protocol), whereas the other method gives your body more fluids (fluid liberal protocol). Both ways are considered standard care. We do no know which way is better for patients."

The revised consent form also contains the following paragraph in the WHAT IS INVOLVED IN THIS Study:

"The fluid management strategies used in this study have been developed by physicians who are considered experts in the care of critically ill patients. These strategies, while similar to those used in routine care, have not been used in patients before. Hence, it is unknown whether the use of these specific strategies is associated with any additional risks. Very close attention will be paid to the safety of these specific fluid management strategies."

We believe that the phrase "One way minimizes (or reduces) the amount of fluids (fluid conservative protocol), whereas the other method gives your body more fluids (fluid liberal protocol)" describes the nature of the experimental design. We also believe that the phrase "These strategies, while similar to those used in routine care, have not been used in patients before," describes qualitatively the relationship between the experimental fluid management interventions and standard fluid management. Since the experimental fluid strategies were developed by practicing clinicians based on their standard care practices, we feel that it is accurate to state that the experimental and standard fluid management strategies were similar. By stating that the strategies have not been used in patients before, we feel that this phrase also points out the experimental nature of the fluid management strategies in the ARDSNet Study 05 (FACTT) protocol. Finally, we feel that because a) "standard fluid management" as well as the management strategies in the ARDSNet Study 05 (FACTT) protocol incorporates a broad range of practices and b) "standard fluid management" strategies are quite variable between physicians, it would be hopelessly futile to be able to describe the exact differences between the experimental and standard fluid management strategies. Any attempt to describe any purported differences between these fluid management strategies would require detail, if it is possible to provide detail, beyond comprehension.

Regarding *"Both types of [fluid management] methods are considered standard of care"* , we agree that this phrase is not optimal. While the specific interventions in the fluid management strategies are considered standard of care, the actual strategies themselves are experimental. Many of the IRB approved consent forms acknowledge the experimental nature of the two treatment arms explicitly. Appropriate changes to consent forms will be proposed to IRBs.

(iii) OHRP is concerned that the sample informed consent document fails to describe the differences between the two experimental fluid management strategies with respect to diuretic dosing and dobutamine dosing. Instead, the informed consent document leaves the impression that the only difference between the fluid conservative

management and fluid liberal management is the amount of fluid administered. Please respond.

We agree that the addition of diuretic dosing and dobutamine language to the consent form is reasonable and will propose to IRBs that the consent forms that do not contain such language be revised.

(iv) OHRP is concerned that the sample informed consent document fails to indicate that all subjects will be required to be placed on a low tidal volume of 6 ml/kg PBW. Please respond.

Many ICUs may specify that ventilation with 6 ml/kg is considered standard of care for all patients. Accordingly, the language in the informed consent will need to be site-specific regarding this issue.

(v) OHRP is concerned that the sample informed consent document fails to describe the plan for obtaining DNA for genetic testing. Please respond.

A separate document was developed for obtaining DNA for genetic testing. A copy is attached in Appendix Q.

(c) HHS regulations at 45 CFR 46. 116(a)(2) require that when seeking informed consent, a description of any reasonably foreseeable risks or discomforts to the subject shall be provided to the subject or the subject's legally authorized representative.

(i) OHRP is concerned that the sample informed consent document fails to include death as one of the risks of the research. In particular, there is no statement that subjects could have a higher risk of death depending on which experimental group they are assigned to, in comparison to each of the other experimental groups and in comparison to not entering the trial and receiving individualized care based upon best clinical judgment. Furthermore, there is no statement that death could result from complications related to the pulmonary artery catheter placement and use. Please respond.

We agree that we did not specifically mention that the risk in the sample informed consent form provided to IRBs and that of death may be higher or lower depending on which experimental group subjects are assigned to and that the risk of death in either of the experimental groups may be higher or lower compared to standard care. However, we feel that it would be inaccurate and misleading to state that standard care consists of "individualized care based upon best clinical judgment." This is because we do not know that best clinical judgment has been applied in each case either because of the treating physician's lack of knowledge or lack of due consideration.

We also acknowledge that there may be a small risk of death from the PA catheter over the benefit gained from the information gained by its use, with a rough estimate of 0.1%. We will recommend to IRBs incorporation of this risk into future FACTT consent forms.

(ii) OHRP is concerned that the sample informed consent document fails to include the risks of having the tidal volume adjusted to 6 ml/kg PBW. These risks appear to include increased probability of developing hypercapnia, respiratory acidosis (requiring more sodium bicarbonate), agitation and dyspnea (requiring greater sedation), and oxidant-induced lung injury secondary to higher FiO2 requirements. Please respond.

Since the publication of the ARDSNet Study 01 (ARMA) trial, many critical care physicians, especially those in the participating ARDSNet ICUs, use or approach the administration of 6 ml/kg tidal volume in many of their patients. Hence, many subjects would receive this tidal volume if not participating in the research. However, we agree that some subjects enrolled in the ARDSNet Study 05 (FACTT) trial might have received a tidal volume that was higher than 6 ml/kg and it is conceivable that receiving a tidal volume of 6 ml/kg might result in risks not associated with the higher tidal volume. However, to achieve a balanced presentation of the risks and benefits of receiving 6 ml/kg tidal volume, we should also include that one of the potential BENEFITS of being in the trial is that one might be removed from exposure to what might be injurious forms of mechanical ventilation, i.e. a higher tidal volume.

(iii) OHRP is concerned that the sample informed consent document fails to describe the risks associated with each of the experimental fluid management strategies. For example, there is no mention that subjects assigned to the fluid conservative management group may experience inadequate organ perfusion which could result in renal failure, ischemic brain injury, cardiac ischemia, or other end organ damage. Likewise, there is no mention that subjects assigned to the fluid liberal group could experience excessive pulmonary edema and delayed lung recovery.

Furthermore, depending on group assignment, subjects may receive higher doses of diuretics and dobutamine than they might receive if they did not enter the clinical trial, yet there is no discussion of the risks of receiving higher doses of these drugs in the sample informed consent document.

We agree that the risks associated with each of the experimental fluid management strategies are missing from the sample informed consent form. Each individual IRB approved the informed consent forms included for OHRP review in Appendix P. Amending consent documents to reflect the risks associated with these strategies, as mentioned in the protocol, will be recommended to IRBs.

We also agree that depending on group assignment, there is a possibility that some subjects might be receiving more frequently (or less frequently) and also higher (or lower) doses of diuretics and dobutamine than they might receive if they did not enter the clinical trial. We will recommend IRB re-review of existing consent forms to see if existing language adequately reflects these possibilities.

(iv) OHRP is concerned that the inclusion of the following statements regarding the fluid management strategies in the WHAT ARE THE RISKS OF THE Study section is misleading and minimizes the potential risks:

"Finally, as part of this study, we are using fluid management strategies…that have been developed by critical care experts. Similar types of fluid management strategies have been used before in patients and are considered standard of care."

Please respond.

We respectfully disagree with this assessment. While these statements by themselves would be considered misleading, when they are considered in light of the other statements in the document, especially the other statements about risks that will now be included as suggested by OHRP, these statements are probably not misleading. Furthermore, the statements reflect facts, as the fluid management strategies were developed by critical care experts and they are similar to other strategies used in standard care practice.

(d) HHS regulations at 45 CFR 46.116 require that the information that is given to the subject or the subject's legally authorized representative shall be in language understandable to the subject or the representative. OHRP is concerned that the language throughout much of the sample informed consent document would not be understandable to most subjects or their representatives. In particular, the descriptions of the research interventions, the alternatives, and the risks and discomforts are confusing and difficult to understand. Please respond.

It is probably not relevant and hence, not worthwhile to respond specifically to the concerns regarding a "sample" consent form for several reasons. First, what counts as being most relevant is the actual language used in the consent forms that have been reviewed by the individual IRBs. Second, the important additions and changes that we agreed are required in these documents will probably make these documents more understandable to potential subjects.

(17) OHRP acknowledges that the final versions of the informed consent documents approved by the ARDSNet institutions' IRBs may have addressed the concerns raised in item (16) above. Please provide a copy of the IRB-approved informed consent documents from each participating ARDSNet institution.

Please see Appendix P.

Appendices:

A. Tables from August 19, 2002 letter from Gordon Bernard, M.D., chair of the NIH NHLBI ARDS Network to James Kiley, Ph.D., Director of the Division of Lung Diseases

B. Michael Young, M.D. manuscript, Ventilation of Patients with Acute Lung Injury

C. Letter from Gordon Rubenfeld, M.D., MSc, director of the King County Lung Injury Project to Gordon Bernard, M.D.

D. ARDSNet Study 01 (ARMA) Data Summary Tables

E. ARDSNet Study 01 (ARMA) screening case report form

F. ARDSNet Study 01 (ARMA) publications and abstracts

G. ARDS Network Informed Consent Process

H. ARDSNet Study 01 (ARMA) informed consent forms from all ARDSNet centers

I. December 16, 2002 letter from Thomas Petty, M.D. to Martin Tobin, editor of the New England Journal of Respiratory and Critical Care Medicine

J. ARDSNet Study 05 (FACTT) Data Summary Tables (CONFIDENTIAL)

K. ARDSNet DSMB report, December 9, 2002 (reviewed by DSMB on December 13, 2002) (CONFIDENTIAL)

L. ARDSNet Study 05 (FACTT) screening case report form

M. ARDSNet Study 05 (FACTT) abstracts

N. ARDSNet Ethics Committee Report, September 14, 2001: Continuing Consent of ARDSNet Research Subjects

O. ARDSNet Study 05 (FACTT) sample informed consent form

P. ARDSNet Study 05 (FACTT) informed consent forms from all ARDSNet centers

Q. ARDSNet Study 05 (FACTT) sample informed consent for optional genetic research on stored tissue specimens, July 5, 2000

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