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RE: Human Research Subject Protections Under Multiple Project Assurances (MPA) M-1331, M-1363, and M-1138 and the OHRP-approved Assurances for all ARDS Network Institutions

Research Project: Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA)
Project Number: ARDSNet Study #01

Research Project: Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter (PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) and Prospective, Randomized, Multi-Center Trial of 'Fluid Conservative' vs. 'Fluid Liberal' Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) (FACCT)
Project Number: ARDSNet Study #05

Research Project: Prospective, Randomized, Multi-Center Trial of Higher End-Expiratory Lung Volume/Lower FiO_2 Versus Lower End-Expiratory Lung Volume/Higher FiO_2 Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome - Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI)
Project Number: ARDSNet Study #04

Dear Drs. Newbower, Limbird, and Kay:

The Office for Human Research Protections (OHRP) has received the enclosed manuscript and complaint letter that raise concerns and allegations of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the ARMA and FACCT clinical trials referenced above.

In July of this year, OHRP transmitted the concerns raised by the authors of the enclosed manuscript and the enclosed complaint letter to officials at the National Heart, Lung, and Blood Institute (NHLBI). NHLBI subsequently communicated most of the concerns that were raised to the ARDS Clinical Network (ARDSNet) investigators for response (see the enclosed sample letter dated July 29, 2002 sent by NHLBI to the ARDSNet investigators participating in the FACCT trial). On July 25, 2002, NHLBI voluntarily placed the FACCT trial on clinical hold pending resolution of the concerns being raised about the above-referenced ARDSNet trials.

OHRP has reviewed the August 19, 2002 report from Dr. Gordon R. Bernard, Chairman, ARDSNet Steering Committee, responding on behalf of the ARDSNet to the concerns raised regarding the ARMA and FACCT trials. OHRP also attended the August 30, 2002 meeting that was convened by NHLBI and involved a panel of five external consultants, key ARDSNet investigators, National Institutes of Health (NIH) Clinical Center staff who authored the enclosed manuscript, and key NHLBI staff.

Based upon its review of relevant ARDSNet protocol documents, selected literature cited in the ARDSNet protocols, Dr. Bernard's report, and the information presented during the August 30, 2002 meeting convened by NHLBI, OHRP continues to have serious unresolved concerns, as outlined below in detail, that the ARMA and FACCT trials failed to comply with key requirements of the HHS regulations for the protection of human subjects. Furthermore, after reviewing documents related to the ALVEOLI clinical trial, which was referenced in Dr. Bernard's report, OHRP has similar concerns about the ALVEOLI trial.

Therefore, consistent with your obligations under HHS regulations at 45 CFR 46.103(a), 46.103(b)(5), and 46.115(b) and under your MPAs, I am requesting that your institutions investigate this matter further, with appropriate input from the other ARDSNet institutions that participated in any of the above-referenced trials, and forward to OHRP a written report of your institutions' investigation (see OHRP Compliance Oversight Procedures dated December 4, 2000 at http://ohrp.osophs.dhhs.gov/references/ohrpcomp.pdf).

Please ensure that your report(s) responds in detail to each of the concerns, questions, and allegations listed below and includes all requested documents and information:

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

(1) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations, the institutional review boards (IRBs) designated under an OHRP-approved assurance shall determine, among other things, that (i) risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose the subjects to risk and (ii) risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.

Given that (i) acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are rapidly lethal disorders with high baseline short-term mortality rates; (ii) the prospective subjects for the research were in nearly all cases not expected to be able to consent on their own behalf; (iii) the subject population was highly vulnerable; and (iv) the primary study endpoint was short-term mortality, OHRP recognizes that it was essential that the ARMA trial satisfy the highest ethical standards and regulatory requirements, particularly those provided for under 45 CFR 46.111(a)(1) and (2). Furthermore, OHRP recognizes that it is of paramount importance that clinical trials involving such a subject population and greater than minimal risk interventions be designed to provide results and conclusions that would be directly relevant to clinical practice, not simply an answer to a physiologic question.

OHRP is concerned that the requirements of 45 CFR 46.111(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 group 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.

(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 (PBW) (with plateau pressures limited to 30 cm H_2O) and 12 ml/kg PBW (with plateau pressures limited to 50 cm H_2O), 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.

(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 judgement of a team of intensive care physicians (hereafter referred to as a "standard of care" tidal volume control group); or

(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.

(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 (6 ml/kg) is superior to either of the following:

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

(ii) mechanical ventilation management with tidal volumes routinely set at a level 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 volume most commonly used in routine clinical practice; and

(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 airway pressures (as high as 50 cm H_2O per the ARDSNet protocol) may have contributed further to an increased risk of death.

(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.

(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.

(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 distribution 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.

(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.

(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.

(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 that participated in the ARMA trial to conduct a review of the clinical records for a representative consecutive sample of patients who were diagnosed 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.

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

(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.

(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.

(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?

(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 this clinical trial in humans?

(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.

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

(a) Site of enrollment.

(b) Date informed consent was obtained and documented.

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

(d) Predicted (or ideal) body weight.

(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, the tidal volumes used, and plateau airway pressures measured.

(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.

(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.

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

(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).

(j) With respect to the 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 were handled in the data analysis.

If any of the above-listed data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

(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 all data collected on all such patients. Again, if any of the this data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

(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.

(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 to or less than 0.007. Furthermore, OHRP notes that the IRB-approved protocol included a plan for interim analyses at 200, 400, 600, 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:

(a) Provide the statistical plan for the interim analyses.

(b) Provide the outcome of each interim analysis by the Data and Safety Monitoring Board (DSMB). Please include the following: date of the DSMB

review; number of subjects enrolled at 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.

(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?

(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.

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

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

(12) OHRP is concerned that the ARMA protocol provided 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; (b) additional safeguards that were to be included for subjects who were likely to be vulnerable to coercion or undue influence; (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 consenting for themselves during the course of the trial; and (d) the basis for excluding pregnant women. Please respond in detail.

(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 (6 ml/kg PBW) versus a high tidal volume (12 ml/kg PBW).

(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).

(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.

(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.

Please respond in detail to each of the above concerns regarding the informed consent documents.

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

(1) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations, the institutional review boards (IRBs) designated under an OHRP-approved assurance shall determine, among other things, that (i) risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose the subjects to risk and (ii) risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.

Given that (i) ALI and ARDS are rapidly lethal disorders with high baseline short-term mortality rates; (ii) the prospective subjects for the research were in nearly all cases not expected to be able to consent on their own behalf; (iii) the subject population was highly vulnerable; and (iv) the primary study endpoint was short-term mortality, OHRP recognizes that it was essential that the FACCT trial satisfy the highest ethical standards and regulatory requirements, particularly those provided for under 45 CFR 46.111(a)(1) and (2). Furthermore, OHRP recognizes that it is of paramount importance that clinical trials involving such a subject population and greater than minimal risk interventions be designed to provide results and conclusions that would be directly relevant to clinical practice, not simply an answer to a physiologic question.

OHRP is concerned that the requirements of 45 CFR 46.111(a)(1) and (2) have not been satisfied for the FACCT 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.

(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 CVP or PAOP in the fluid liberal experimental group, and (ii) excluded a control arm maintained on target CVPs or PAOPs 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.

(c) The FACCT 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 [sic] potential**

risks, in that these specific strategies have not been tested in patients previously." [emphasis added]

(d) Because of the apparent failures noted in (a) and (b) above, and the information cited in (c) above, the FACCT 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 PAOPs 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 judgement 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, 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).

(e) As a result of (a)-(d) above, it appears that after the completion of the FACCT, 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.

(f) As a result of (a)-(d) above, both groups of experimental subjects in the FACCT 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).

(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 FACCT study design to include either a "standard of care" fluid management control group or an "average" fluid management control group.

(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 the 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 allow 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 patient. Presumably, such routine clinical practice does 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.

(2) Please clarify whether or not, prior to designing the FACCT 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 FACCT 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.

(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.

(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.

(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 FACCT 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.

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

(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.

(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 the likelihood of showing a statistically significant difference between the two experimental groups?

(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? If so, please provide relevant literature. If not, did the ARDSNet investigators consider conducting such animal studies before initiating this clinical trial in humans?

(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 FACCT protocol provides a theoretical basis for why each of the experimental fluid management strategies selected for the FACCT 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.

(7) OHRP is concerned that the BACKGROUND section of the FACCT protocol provides little, if 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.

(8) OHRP notes that the FACCT protocol stipulates that all subjects are to be placed on low tidal volume protocol (6 ml/kg PBW). As noted above 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 PBW may pose 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 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.

(9) Please provide a complete list of all ARDSNet institutions participating in the FACCT 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.

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

(a) Site of enrollment.

(b) Date informed consent was obtained and documented.

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

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

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

(f) Predicted (or ideal) body weight.

(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 airway pressures measured.

(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.

(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.

(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.

(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).

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

(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.

(n) With respect to the 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.

If any of the above-listed data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

(11) Please clarify whether the participating ARDSNet sites for the FACCT 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. Again, if any of the this data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

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

(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:

(a) Date of the DSMB review.

(b) Number of subjects enrolled at 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.

(14) OHRP is concerned that the FACCT 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; (b) additional safeguards that were included for subjects who were likely to be vulnerable to coercion or undue influence (e.g., independent consent monitors); (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 consenting for themselves during the course of the trial; (d) whether the research satisfies the requirements under HHS regulations at 45 CFR Part 46, Subpart D, for research involving children; and (e) the basis for excluding pregnant women. Please respond in detail. In your response, please clarify whether the IRB at any site requested and received supplemental information that addressed these issues. If so, please identify the institutions and provide copies of the supplemental information that was provided to the IRB.

(15) OHRP notes that the inclusion criteria in the FACCT 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 Part 46, 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.

(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 retained this language in the 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.

(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.

(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.

(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.

(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.

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

(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 judgement. Furthermore, there is no statement that death could result from complications related to the pulmonary artery catheter placement and use. Please respond.

(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 FiO_2 requirements. Please respond.

(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. Please respond.

(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.

(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.

(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.

C. Concerns and questions regarding the ALVEOLI trial (ARDSNet Study #04):

(1) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations, the institutional review boards (IRBs) designated under an OHRP-approved assurance shall determine, among other things, that (i) risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose the subjects to risk and (ii) risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.

As with the ARMA and FACCT trials, OHRP is concerned that the requirements of 45 CFR 46.111(a)(1) and (2) were not satisfied for the ALVEOLI 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 PEEP and FiO_2 on which patients were maintained during routine clinical practice at the participating ARDSNet study sites.

(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 PEEP/high FiO_2 target levels in one experimental group and high PEEP/low FiO_2 in the other experimental group, and (ii) excluded a control arm managed with target levels of PEEP and FiO_2 set at levels somewhere in the mid-range of these treatment parameters that would have encompassed the levels of PEEP and FiO_2 most frequently used in routine clinical practice at the time the study was initiated.

(c) Because of the apparent failures noted in (a) and (b) above, the ALVEOLI 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 ventilation management with target PEEP and FiO_2 levels 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 judgement of a team of intensive care physicians (hereafter referred to as a "standard of care" PEEP/FiO_2 control group); or

(ii) protocol-mandated ventilation management with target PEEP and FiO_2 levels set at target levels representing, as appropriate based upon systematic assessment of routine clinical practice, the mean, median, mid-range or mode of PEEP and FiO_2 levels used in routine clinical practice at the time the study was conducted (hereafter referred to as an "average" PEEP/FiO_2 control group).

(d) As a result of (a)-(c) above, it appears that the ALVEOLI study would not have been able to provide sufficient evidence to support any conclusion that either the low PEEP/high FiO_2 or high PEEP/low FiO_2 management strategy is superior either of the following:

(i) Individualized "standard of care" PEEP/FiO_2 management; or

(ii) a ventilation management strategy with target PEEP and FiO_2 levels set at any other level between those defined by the two experimental groups.

(e) As a result of (a)-(c) above, both groups of experimental subjects in the ALVEOLI study may have been placed at an increased risk of death in comparison to patients managed according to a "standard of care" PEEP/FiO_2 control group strategy or an "average" PEEP/FiO_2 control group strategy because:

(i) the two experimental groups received mechanical ventilation with PEEP and FiO_2 levels set at levels that may have been lower or higher than the levels of PEEP and FiO_2 most commonly used in routine clinical practice; and

(ii) the relationship of mortality to PEEP and FiO_2 levels may be quadratic, resulting in a U- or J-shaped curve.

(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 ALVEOLI study design to include either a "standard of care" PEEP/FiO_2 control group or an "average" PEEP/FiO_2 control group.

(g) OHRP acknowledges that the target levels for PEEP and FiO_2 used for the two experimental groups may be 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 ventilation management strategies that allow individualized target levels of PEEP and FiO_2 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 patient. Presumably, such routine clinical practice does not result in assignment of patients to ventilation management strategies under which target levels of PEEP and FiO_2 are set at a high or low levels based upon random choice.

Please respond in detail to each of the above items.

(2) Please clarify whether or not, prior to designing the ALVEOLI 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 distribution of PEEP and FiO_2 levels used in actual clinical practice

to treat the type of patient population that would have been eligible for the ALVEOLI 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.

(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.

(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.

(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 that participated in the ALVEOLI trial to conduct a review of the clinical records for a representative consecutive sample of patients who were diagnosed 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.

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

(c) A frequency distribution of the PEEP, FiO_2, and PEEP:FiO_2 ratio measured on days 1, 3, 7, and 14 of ventilator therapy for each ARDSNet study site and for all sites combined.

(4) Please explain the basis for selecting the two experimental groups (low PEEP/high FiO_2 and high PEEP/low FiO_2). Was there any basis pre-study to assume that the two PEEP/low FiO_2 management strategies would be safer and more effective than strategies using levels of PEEP and FiO_2 in the middle of range bracketed by the two experimental groups? Were the PEEP and FiO_2 levels 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?

(5) Did the ARDSNet investigators take into account any animal studies assessing the mortality rate of animals assigned to multiple different target levels of PEEP and FiO_2 over a wide range of each of these variables? If so, please provide relevant literature. If not, did the ARDSNet investigators consider conducting such animal studies before initiating this clinical trial in humans?

(6) Please provide evidence from any human studies that supports the conclusion that the two PEEP/FiO_2 ventilation strategies selected for the ALVEOLI trial were safer or more effective than either a "standard of care" PEEP/FiO_2 control group strategy or a PEEP/FiO_2 control group strategy. In providing your response, please note that the IRB-approved ALVEOLI protocol provided a theoretical basis for why each of the experimental PEEP/FiO_2 strategies selected for the ALVEOLI trial may be less advantageous than a ventilation strategy that is either individualized or attempts to maintain PEEP and FiO_2 levels in the middle of the ranges of these parameters used in routine clinical practice.

(7) OHRP notes that the ALVEOLI protocol stipulated that all subjects were to be placed on low tidal volume protocol (6 ml/kg PBW). As noted above in section A, there appears to have been 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 PEEP/FiO_2 ventilation 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 PBW may pose 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 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.

(8) Please provide a complete list of all ARDSNet institutions that participated in the ALVEOLI 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.

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

(a) Site of enrollment.

(b) Date informed consent was obtained and documented.

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

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

(e) Predicted (or ideal) body weight.

(f) 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, the plateau airway pressures measured, the PEEP, and the FiO_2.

(g) 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.

(h) The following baseline data: age, gender, systemic systolic and diastolic blood pressure, heart rate, APAHCE III score, mode of ventilation, tidal volume, plateau airway pressure, peak inspiratory pressure, PEEP, FiO_2, PaO_2, SpO_2, pCO_2, arterial pH, serum electrolytes, BUN, creatinine, hematocrit/hemoglobin, CVP, and PAOP.

(i) The following data for each day post randomization for which data was collected: systemic systolic and diastolic blood pressure, heart rate, mode of ventilation, tidal volume, plateau airway pressure, peak inspiratory pressure, PEEP, FiO_2, PaO_2, SpO_2, pCO_2, arterial pH, hemoglobin, and requirements for sedatives/tranquilizers/neuromuscular blocking agents/vasopressors.

(j) Data regarding number of times the protocol-mandated PEEP/FiO_2 ventilation strategy was overridden by the primary healthcare provider and reasons for each override.

(k) Data with respect to the following outcomes variables: vital status at 28 and 60 days, time to initiation of unassisted breathing, status 48 hours after initiation of unassisted breathing, study day number post randomization when discharged from ICU, and study day number post randomization when discharged from hospital.

(l) With respect to the 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.

If any of the above-listed data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

(10) Please clarify whether the participating ARDSNet sites for the ALVEOLI 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. Again, if any of the this data is available in an electronic or digital format, please provide the data via electronic or digital media, with an explanation of the appropriate software needed to access the data.

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

(12) 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:

(a) Date of the DSMB review.

(b) Number of subjects enrolled at 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 (9)(k) above; and statistical tests used and p values for the comparison of each endpoint measurement between the two experimental groups.

(13) OHRP is concerned that the ALVEOLI protocol provided little substantive discussion of the multiple complex ethical issues related to human subject protections that are presented by such research. For instance, the protocol did 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; (b) additional safeguards that were included for subjects who were likely to be vulnerable to coercion or undue influence (e.g., independent consent monitors); (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 consenting for themselves during the course of the trial; (d) whether the research satisfies the requirements under HHS regulations at 45 CFR Part 46, Subpart D, for research involving children; and (e) the basis for excluding pregnant women. Please respond in detail. In your response, please clarify whether the IRB at any site requested and received supplemental information that addressed these issues. If so,

please identify the institutions and provide copies of the supplemental information that was provided to the IRB.

(14) OHRP notes that the inclusion criteria in the ALVEOLI protocol allowed for subjects as young as 13 years to be enrolled in the trial. OHRP is concerned that the research may have failed to satisfy the requirements of HHS regulations at 45 CFR Part 46, 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.

(15) Please provide a copy of the IRB-approved informed consent documents from each participating ARDSNet institution. Please review these informed consent documents and determine whether the concerns raised by OHRP regarding the ARMA and FACCT informed consent documents also apply to the ALVEOLI trial. If so, please respond to these concerns.

If your investigation of the above concerns, questions and allegations reveals noncompliance, please provide a description of any corrective actions that have been or will be taken by the ARDSNet institutions to correct the noncompliance and/or prevent such noncompliance from recurring.

Please forward your report so that OHRP receives it no later than December 6, 2002.

It is OHRP's understanding that NHLBI has maintained the voluntary clinical hold on the FACCT trial. Please be aware that OHRP expects the clinical hold to remain in effect until OHRP's concerns regarding the trial are resolved and OHRP's evaluation of this matter has been completed.

OHRP appreciates the continued commitment of your institutions to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

Enclosures: Metaanalysis manuscript
Correspondence from complainant
Initial concern letter from NHLBI
FACCT sample informed consent document

cc with enclosures:

Mr. Harold J. DeMonaco, Chairperson, IRB, Massachusetts General Hospital
Dr. B. Taylor Thompson, ARDS Net Coordinating Center Principal Investigator, Massachusetts General Hospital
Mr. William A. Mountcastle, Director, Nashville Veterans Affairs Medical Center
Dr. Mark Magnuson, Assistant Vice Chancellor for Research, Vanderbilt University
Dr. Margaret Rush, Chairperson, IRB-01, Vanderbilt University
Dr. William Cooper, Chairperson, IRB-02, Vanderbilt University
Dr. Arthur Wheeler, FACCT Trial Committee Chair, Vanderbilt University
Dr. Gordon R. Bernard, Chairman, ARDS Steering Committee, Vanderbilt University
Dr. Alan Lichtin, Chairperson, IRB, Cleveland Clinic Foundation
Dr. Herbert P. Wiedemann, FACCT Trial Committee Chair, Cleveland Clinic Foundation
Dr. John Mather, ORCA, Department of Veterans Affairs

cc without enclosures:

Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Dr. Irene Stith-Coleman, OHRP