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March 12, 2003

Michael A. Carome, MD
Director, Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Dr. Carome:

This cover letter and the attached document are being provided in response to your letter of October 7, 2002. You agreed, in your communication of December 12, 2002, to defer consideration of the ARDSNet Study 04 (ALVEOLI) trial while we explore the issues raised by OHRP regarding the ARDSNet Study 05-Fluid And Catheters Treatment Trial (FACTT) and ARDSNet Study 01-Acute Respiratory Management in ALI/ARDS (ARMA) trials. Enrollment of subjects in the ARDSNet Study 05 (FACTT) trial is still temporarily on hold by the Lung Division of the NHLBI, pending your review and in accordance with your wishes. The ARDS Network investigators recognize that ethical research must address valuable questions, be conducted in a methodologically rigorous manner, generate valid scientific knowledge, produce results that can advance the health of society, and be based on accepted clinical and research principles, methods, and practices. Research subjects can be exposed to risks only when research meets these requirements and can thereby be deemed ethical.

When the ARDS Network was first created, it was the initial intent to conduct trials of pharmacologic interventions designed to improve the outcomes of patients with ALI/ARDS. However, during organizational meetings in 1994-1995 we explored a substantial body of evidence (primarily from laboratory studies in animals) that suggested ventilator management, specifically, tidal volume and inspiratory pressure, might alter patient outcomes. Despite the animal data and uncontrolled human studies, many clinicians doubted the value of volume-and-pressure limited ventilation in changing the outcome of patients with ALI/ARDS. Some argued that commonly recommended larger tidal volumes (and high airway pressures) improved oxygenation, dead-space ventilation, and acid-base homeostasis, producing at least short-term clinical benefits. Others argued that in spite of short-term benefits there was reason to believe that lung injury from larger tidal volumes (and higher airway pressures) might lower patient survival. Lower tidal volume ventilation strategies were proposed by clinicians to avoid this lung injury, even though oxygenation, dead-space ventilation, and acid-base homeostasis might appear less favorable during early patient care. Variation in ventilator management practices across the country reflected a lack of both physician consensus and understanding about the best clinical mechanical ventilation management strategy for ALI/ARDS patients. As shown in the attached document, tidal volumes prescribed by physicians for ALI/ARDS patients spanned a broad range, and there was no discernible difference in the distributions of tidal volumes across

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an equally broad range of associated inspiratory plateau pressures. Moreover, there is little to no evidence that tidal volumes were adjusted over time in individual patients. These observations suggest that tidal volumes were not selected or adjusted in relation to physiologic considerations specific to individual patients.

The ARDS Network provided, for the first time, sufficient resources to conduct a scientifically rigorous large-scale clinical trial to attempt to determine which of the above described strategies were best for patients. By examining larger and smaller tidal volume strategies, we expected to improve the care of the greatest number of patients because almost all ALI/ARDS patients require mechanical ventilation.

In the attached response, we will discuss in detail the information used to design the ARDSNet Study 01 (ARMA) trial. We will review the extensive body of evidence demonstrating that the larger tidal volume strategy we studied was within a clinically recommended range for tidal volumes, was reported to be used in the majority of respondents to an international survey, and was indeed used by clinicians caring for patients with ARDS in clinical trials in the early 1990's, prior to the design of ARDSNet Study 01 (ARMA). Furthermore, we show that in one-fifth of cases clinicians selected a tidal volume of 12 ml/kg PBW or higher as part of routine care prior to entry into the ARDSNet Study 01 (ARMA). We also review the evidence suggesting that the lower tidal volume we studied in the ARMA trial appeared to be safe and appropriate to carry forward to a Phase III trial. We describe in detail our rationale for not including an uncontrolled mechanical ventilation group in our trial design. Furthermore, we explain how we minimized risks to research participants through a number of mechanisms, including attending physician approval for all patient participation and ICU clinician oversight of all ARDSNet Studies 01 (ARMA) and 05 (FACTT) protocol recommendations.

We have highlighted some issues that we believe deserve careful attention and consideration as OHRP reviews the attached response in its entirety.

5. Issues Regarding the Requested Chart Reviews

A. ARDS Network Request to Defer Chart Review

We previously asked OHRP to consider deferring the requirement for extensive chart reviews regarding ventilator and fluid management practice patterns at the ARDSNet clinical sites pending review of existing data. OHRP indicated it did not wish to change the Oct. 7 letter request for the chart review so the ARDSNet has begun organizing the process for the chart review. However, in trying to formulate a plan to accomplish this task, it has become clear that the data obtained in this way will be limited to measurements made within 36-48 hours of study patient enrollment.

OHRP requested a retrospective review of ARDS Network ICU patient medical records to establish tidal volume, plateau pressure, central venous pressure and pulmonary artery occlusion pressure ranges and goals used in clinical practice. This would address a topic that has already been systematically evaluated in the literature. We fear that such a chart review would produce

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only limited data that would not further our or your understanding, compared with the data already published and included in Tables 1, 2, and 3 of the August 19, 2002 letter from Gordon Bernard, M.D. (Chairman of the NIH NHLBI ARDS Network) to James Kiley, Ph.D., Director of the Division of Lung Diseases. Most of these published studies came from ICUs similar to those of the ARDS Network investigators.

The published literature, our collective observations and those of our colleagues, indicated that selections of tidal volumes and inspiratory pressures as well as goals for circulatory volume status in routine clinical practice were highly variable. To study these issues in ARDSNet Studies 01 (ARMA) and 05 (FACTT), we designed protocols to compare higher and lower tidal volume and IV fluid support strategies.

Again, we ask OHRP, after reviewing the attached report, to reconsider the need for chart review.

B. Issues Identified During Preparation for Chart Review

As we prepared to conduct the retrospective medical record reviews and data collection, we noted additional issues which we believe significantly limit conclusions that could be drawn from such a chart review. The specific issues are discussed below.

1. Match Clinical Practice

With regard to collection of tidal volume targets, plateau pressures, CVP and PAOP targets, it is important to note that we acknowledge that our study arms in ARDSNet Studies 05 (FACTT) and 01 (ARMA), though representing large components of routine practice, were not designed to match, and will not match, the mean, median or mode of routine practice for several reasons. First, our overall design philosophy was to examine two strategies for ventilator management based on higher or lower tidal volumes (as tested in Phase II trials, some with data publicly available but not yet published at the time ARMA was designed) and two strategies for fluid management. Either of these interventions could have led to more favorable patient outcomes or they could have been equivalent. Second, as noted in our attached response and in Section 1.1.1 of the original ARDSNet Study 01 (ARMA) protocol, we relied on published recommendations for ventilator and fluid management, on an international survey of physician preferences, on actual tidal volumes selected during clinical care in studies conducted in the early 1990's, on three small clinical trials of 6 ml/kg PBW tidal volume, and on our individual experiences as intensive care clinicians.

As will be shown in the attached document, tidal volumes prescribed by physicians spanned a broad range, and there was no discernible change in the distribution of these tidal volumes over time or across a broad range of associated inspiratory pressures. These observations suggest that tidal volumes were selected randomly rather than by systematic choice based on physiologic considerations.

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2. Protocols and Variability

A protocolized approach produces marked reductions practice variation so that while matching the mean or average of practice is theoretically possible, matching the variance is difficult to impossible. For example, if mean tidal volume were 12 ml/kg predicted body weight (PBW) in routine practice as well as in our study, the variance around this value would be substantially different because in routine practice, tidal volumes of 4, 5, 6, ...14, 15, etc. ml/kg PBW would be included in the clinical practice mean but would be very infrequent in the study population mean due to protocolization around 12 ml/kg PBW. In a similar vein, we think it is almost guaranteed that clinical practice will vary from one ARDS Network institution to the next. Thus, published literature will provide the information requested by the OHRP in a more comprehensive and reliable manner than that which we could provide with a retrospective medical record review.

3. Baseline Data

ARDS Network pre-randomization baseline tidal volume data show that more than one fifth of patients were ventilated with tidal volumes of 11.8 ml/kg PBW or greater. The actual tidal volume delivered in the higher tidal volume arm of ARMA was 11.8 ml/kg PBW which was well within one standard deviation of the baseline (pre-randomization) mean for these patients (10.3 +/- 1.9). One third of the study patients had plateau pressures of 33 cmH_20 or greater prior to randomization, the mean plateau pressure observed in the higher tidal volume strategy in ARDSNet Study 01 (ARMA). This information is in accordance with published recommendations and is consistent with clinical practice in the early 1990's across the United States. Thus, a strategy similar to the higher tidal volume arm of ARDSNet Study 01 (ARMA) appears to have been used as part of clinical care by a significant portion of clinicians participating in or providing patients to the ARDSNet Study 01 (ARMA). This evidence also indicates that a protocol designed to deliver tidal volumes of 9 ml/kg PBW, for example, would not match routine practice significantly better than the 12 ml/kg selected for ARDSNet Study 01 (ARMA) because it would not match (represent) this group.

4. Pre-Randomization Data From Chart Review

Data for 7 days prior to randomization has been requested by OHRP for ARDSNet Studies 01 (ARMA) and 05 (FACTT) enrolled patients. An analysis of our database indicates that patients in ARMA received mechanical ventilation for only 1.3 +/- 1.5 days prior to study entry (mean +/- sd) and patients in ARDSNet 05 (FACTT) had their central venous catheter only 1.7 +/-1.3 days prior to study entry. Both trials had a prescribed time window for enrollment (36 hours for ARMA and 48 hours for FACTT). Any ventilator data before these time points reflect either a protocol violation (rare) or would represent treatment for conditions *other than ALI* (e.g., sepsis, unilateral pneumonia, trauma, or other risk factors for the development of ALI). These data will not accurately reflect clinical care of patients with ALI. Thus the baseline data for ARDSNet Studies 01 (ARMA) and 05 (FACTT), which were collected immediately prior to the implementation of study related ventilator or fluid management instructions, would provide most of the information available regarding routine care. This information is readily available and is being provided in the attached report.

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We have not yet begun data collection at each ARDS Network center. We estimate the data collection process and review by OHRP will add 3-4 months to the 6 months the ARDSNet Study 05 (FACTT) trial has already been on hold. We prefer, consequently, to discontinue the chart review if it does not add materially to the findings or determinations in the OHRP inquiry. We believe the attached detailed responses and the attached baseline data may adequately address OHRP's concerns. We respectfully request that OHRP reconsider the request for these time consuming chart reviews requested in A(3), A(8)e, B(3), and B(10)g,h after completing its review of our initial response in case there is consensus on the relative value of these reviews. The ARDSNet investigators are concerned about the time element because patients in routine practice may be continuing to be exposed to potentially harmful fluid management strategies until the important management questions posed in the FACTT trial are addressed.

We are developing a centralized plan and rule-set to coordinate the chart review pending OHRP's decision. We await your reconsideration of the need for a retrospective chart review and hope the rationale provided above and the data associated with this letter will clarify important issues during your review of this issue. We request a rapid response from OHRP so we may complete the chart review expeditiously, if OHRP's needs have not been met by the information in this letter and accompanying documents. In making this determination, please note that we do not claim that our study arms necessarily match the mean, median or mode of routine practice, only that our protocol arms operate well within the broad range of practice as detailed above and in the attached document.

3. Issues Regarding the Central Concern of Study Design

A. A priori assumptions: As will be explained in detail in the enclosed document, there was ample evidence in 1995 against a U-shaped relationship of mortality versus tidal volume/plateau pressure. Therefore, there were three possible scenarios regarding the mortality versus tidal volume relationship:

1. Tidal volumes between 6 and 12 ml/kg do not affect mortality.
2. Mortality increases as tidal volumes increase from 6 to 12 ml/kg.
3. Mortality decreases as tidal volume increases from 6 to 12 ml/kg.

Then the best trial, assuming that appropriate a priori considerations have been given to human subject protections, will be a comparison of 6 vs. 12 because such a trial will expose as few patients as possible to an inferior treatment and stop the soonest if differences between groups are observed.

If 6 ml/kg versus 10 ml/kg were tested and no difference in outcome were observed, physicians would think volume is not important and continue to use a broad range of tidal volumes including 12 ml/kg as surveys from the mid 1990's demonstrate.

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There are many questions a trial could ask, and each requires a different design. ARDSNet decided that the broad question, "Does tidal volume matter", was the most important question. After showing that 6 ml/kg is safer than 12 ml/kg, some have asked if perhaps an intermediate tidal volume is as good or better than 6 ml/kg. But this latter question is legitimate only after it is known that tidal volume matters. It is very tempting now in retrospect to assume that physicians knew or should have known that tidal volume and inflation pressures affected survival. However, this information could not be known until the results of ARDSNet Study 01 (ARMA) were released.

B. Description of ventilator practices in the community:

An underlying theme in the discussions between ARDSNet and OHRP centers on "best practices" versus "standard of care" in the critical care community. Deborah Cook, MD, Editor of the "Caring for the Critically Ill" section of the Journal of the American Medical Association and participant in the independent panel review of August 30, 2002, defined these two concepts below.

1) Evidence-based practice (also known as best practice): Treatment that is based on evidence from a large randomized trial which defined and ensured a ventilation or fluid management strategy that was ultimately proven to be superior with respect to pre-specified and compelling clinical outcomes. Such randomized trials were not available at the time that ARDSNet Studies 01 (ARMA) and 05 (FACTT) were being designed and conducted.

2) Routine practice (also known as standard practice): Practice described by observational data (utilization reviews, prospective or retrospective cohort studies, and/or surveys of standard practice) recording current mechanical ventilation practices. OHRP used the term "routine care" interchangeably with "standard of care" in its October 7, 2002 letter to ARDS Network. We prefer "routine care" because the term "standard" implies standardized or otherwise correct practice in the case of mechanical ventilation and fluid therapy. Mechanical ventilation and fluid therapy practice are highly variable, difficult to describe and not evidence based (because there is no high level evidence to support current uncontrolled practice).

3) OHRP defined "Standard of care": In its October 7, 2002 letter, OHRP defined "Standard of care" as individualized mechanical ventilation management with tidal volumes and plateau 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. This definition appears to merge "routine practice" and "evidence-based practice" into a single concept. We respectfully disagree with this concept. As Dr. Cook wrote in her review of this issue, best practice is evidence-based and "it is a mistake to merge these two concepts as they are clearly separate." There is a large body of literature documenting the lack of congruency between evidence-based and routine (uncontrolled) practice. The ARDS Network investigators provide data in the attached responses supporting our conclusion that there was no recognized evidence-based practice for mechanical ventilation at the time ARDSNet Study 01 (ARMA) was being designed and conducted. Instead,

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there was routine practice that was highly variable from center to center and from ICU to ICU. It was impossible to describe in a scientifically and clinically sound manner the method of routine practice except in the most general terms – general terms not useful for a method in a clinical investigation control group. In ARDSNet Study 01 (ARMA), we compared two competing ventilator management strategies to provide clinicians, for the first time in the history of critical care research, high-level evidence to guide ventilator management. This is a marked and important advance in the evolution from routine practice to evidence-based practice. A similar experimental design is being employed in ARDSNet Study 05 (FACTT).

4. Confidentiality Requirement

Please be fully aware that the material herein is *highly confidential* and, in some cases, has been obtained with the formal understanding that it will be disclosed only to official members of the investigation. There are certain components of the ARDSNet Study 05 (FACTT) data reports that have only been seen by the DSMB and a small number of NHLBI and Coordinating Center staff but not by ARDSNet clinical investigators. Because disclosure of these data would be extremely prejudicial to its scientific validity and would likely preclude the resumption of ARDSNet Study 05 (FACTT), we ask OHRP and its designated reviewers to keep the data strictly confidential. We respectfully request that this report not be shown to anyone outside of the official OHRP investigation.

We specifically request that *ad hoc* reviewers who may serve as consultants to the OHRP in this process not include persons who have already gone on record publicly, including publishing their fundamental disagreement with the study designs used by ARDSNet. This would include, for example, Dr. Eichacker and his colleagues at the Clinical Center of the NIH. The concern is that persons who have already made public their opinion on this issue may have a vested interested in the outcome of this review. This would raise questions about their impartiality and reliability as reviewers.

We understand that you have an obligation to protect patient safety in clinical trials across the United States, and to fully investigate all allegations of noncompliance with Federal regulations. This is an important and challenging task and we wish to assist you in discharging this responsibility. To this end, we have provided additional information to our response to assist your review, including summary tables, analyses, and commentary on requested data elements and we have enclosed a copy of the December 9th ARDSNet Study 05 (FACTT) DSMB report. This 144-page report synthesizes large volumes of data related to this complex trial that we hope you will find useful and treat this information with strict confidentiality.

The ARDSNet investigators take our responsibility to ensure patient safety very seriously and we look forward to working with you to resolve the questions and allegations brought forward in your October 7, 2002 letter. We are prepared on short notice to meet with OHRP directly and in person to go over questions that may surface as OHRP conducts its review.

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Sincerely,

Gordon R. Bernard /NSR

Gordon R. Bernard, M.D.
Chairman, ARDSNet Steering Committee
National Institutes of Health (NHLBI) ARDS Clinical Trials Network
Melinda Owen Bass Professor of Medicine,
Vanderbilt University School of Medicine

Enclosures:

1. ARDSNet Investigators' response to OHRP October 7, 2002 letter (74 pages total)
2. Appendices to Investigators' response (Lettered A-Q; 17 total)
3. CD of requested data for enclosed response

Cc: with full enclosures: Dr. James P. Kiley, Director, Division of Lung Diseases, NHLBI

Cc: with selected enclosures (FACTT outcome data have been omitted):

1. ARDSNet Investigators' response to OHRP October 7, 2002 letter (74 pages total)
2. (Selected) Appendices to Investigators' response (A-G, I, L-O, Q; 13 total)

Mr. Roy Nelson, IRB Chairman, McKay-Dee Hospital
Dr. Wesley Byerly, Director, Wake Forest University
Dr. Sue Carlisle, University of California
Dr. David Cornblath, IRB Chairman, Johns Hopkins Hospital
Dr. Robert Edelman, University of Maryland
Dr. John Falletta, IRB Chairman, Duke University
Dr. Jennifer Fischbach, IRB Chairperson, LDS Hospital
Dr. Warren Foote, IRB Chairman, Baystate Medical Center
Ms. Ina Freidman, Tulane University Medical Center
Dr. John Goff, IRB Chairman, St. Anthony's Hospital
Ms. Susie Hoffman, Director, Human Investigation Committee, University of Virginia
Ms. Lisa Jensen, Director COMIRB, University of Colorado Health Sciences Center
Dr. George Kalf, Director, Division of Human Subjects Protection, Thomas Jefferson University
Mr. Regis Kelly, Executive Vice Chancellor, University of California, San Francisco
Dr. Michael Klag, Vice Dean for Clinical Research, Johns Hopkins Hospital
Dr. Kenneth Kratz, Louisiana State University Health Sciences Center
Dr. Alan Lichtin, IRB Chairman, Cleveland Clinic Foundation
Dr. Peter Loewen, Chair, UBC Clinical Research Ethics Office, Vancouver General Hospital
Ms. Helen Mcgough, Director of Human Subjects Division, University of Washington
Dr. Jonathan Moss, IRB Chairman, University of Chicago

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Dr. Richard Re, Ochsner Foundation Hospital
Dr. Steven Shalansky, REB Chair, St. Paul's Hospital
Dr. Joseph Sherwin, Director, Office of Regulatory Affairs, University of Pennsylvania Health System
Dr. Donald Smith, IRB Chair, Moses Cone Health System
Dr. Lew Smith, Executive Director, Office for the Protection of Research Subjects, Northwestern University
Dr. Vernon Sondak, IRB Co-Chair, University of Michigan
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Dr. Ronald Newbower, Senior Vice President for Research and Technology, Massachusetts General Hospital
Dr. Lee Limbird, Associate Vice Chancellor for Research, Vanderbilt University
Dr. Robert Kay, Vice Chairman, Board of Governors, The Cleveland Clinic Foundation