DEPARTMENT OF HEALTH & HUMAN SERVICES

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July 25, 2003

Ralph Snyderman, M.D.
Chancellor for Health Affairs
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Duke University Health System, Inc
DUMC 3701
Durham, North Carolina 27710

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1106

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 Trial)
Principal Investigator: William Fulkerson, M.D.

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) (FACTT Trial)
Principal Investigator: Neil MacIntyre, M.D.

Dear Dr. Snyderman:

The Office for Human Research Protections (OHRP) has reviewed Dr. Gordon Bernard's March 12, 2003 letter submitted on behalf of the ARDS Network investigators, the March 12, 2003 ARDS Network Investigators' Response to the October 7, 2002 OHRP letter, and Duke University Health System's (DUHS) April 8 and April 28, 2003 reports responding to allegations and concerns of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects involving the above-referenced research.

As part of its evaluation of the above-referenced research, OHRP engaged eight external consultants with expertise spanning the areas of human subject protections, bioethics, critical care and pulmonary medicine, and biostatistics. Furthermore, on June 10, 2003, OHRP staff and consultants conducted face-to-face interviews with the complainants who initially brought concerns and allegations about the ARDS Network trials to OHRP's attention and with several senior investigators from the ARDS Network.

Based upon its review, OHRP makes the following determinations regarding each of the above-referenced ARDS Network trials.

OHRP Findings Regarding the ARMA Trial

(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 board (IRB) 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. In order for the IRB to make these required determinations, the IRB necessarily must be able to identify and assess accurately the risks to participating subjects.

(a) In its October 7, 2002 letter regarding the ARDS Network clinical trials, OHRP presented the concern that the ARMA trial failed to satisfy the requirements of 45 CFR 46.111(a)(1) and (2) because the trial (i) included two experimental groups (defined by a target tidal volume of 12 ml/kg predicted body weight (PBW) with plateau pressures limited to $\leq$ 50 cm H_2O in one group and a target tidal volume of 6 ml/kg PBW with plateau pressures limited to $\leq$ 30 cm H_2O in the second group); (ii) lacked a "routine care" control group managed with either individualized target tidal volumes and plateau pressures based upon physician clinical judgement or target tidal volumes from an intermediate level between 6 and 12 ml/kg PBW representative of the target tidal volumes used most frequently in patients with ALI and ARDS during routine clinical practice at the time the study was initiated; and (iii) as a result of (i) and (ii), lacked an adequate plan to monitor for harm to subjects in each experimental study group (i.e., a potentially increased mortality rate in comparison to not participating in the research).

With regard to whether the design of the ARMA trial actually failed to minimize risks to subjects or whether the risks of participation in the trial actually were unreasonable in relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result, almost all of the consultants engaged by OHRP opined that risks to subjects participating in the ARMA trial were minimized and reasonable in

relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result. OHRP believes, however, that the interests of future human subjects would be served best by further discussion within the scientific and bioethics communities about issues regarding appropriate research design in the absence of a standard of care that have been raised in the context of OHRP's compliance oversight evaluation of the ARMA trial. OHRP encourages such discussions.

(b) OHRP finds that when reviewing and approving the ARMA trial, the DUHS IRB failed to receive or request sufficient information to make the determinations required under 45 CFR 46.111(a)(1) and (2).

In particular, OHRP finds that in order to have determined whether the risks to the subjects were minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may have reasonably been expected to result, the DUHS IRB should have received information adequate to assess the risks and potential benefits of each of the interventions for each arm of the ARMA trial relative to concurrent routine clinical practice outside of the research context. OHRP further finds that at least the following additional information would have been needed to make these determinations:

(i) A clear, detailed description of concurrent routine clinical practice at the ARDS Network trial sites with respect to management of tidal volume in patients with ALI and ARDS, including the various clinical factors that effect clinical decision-making related to the adjustment of tidal volume in response to the level of plateau pressure and other clinical parameters. OHRP suggests that, ideally, this description would have included a frequency distribution of actual tidal volumes used and plateau pressures measured in patients with ALI and ARDS over the course of their illness in routine practice at the institutions where the ARMA study was to be conducted.

(ii) A detailed comparison of the tidal volume management strategies that were to be used in the two experimental groups relative to concurrent routine clinical practice, particularly with respect to the upper limits of plateau pressure that were to be permitted for each group.

(iii) A description and analysis of morbidity and mortality data from the two pilot studies described in the Background section of the ARMA protocol.

(iv) A more detailed description of the data and safety monitoring plan for the trial, including a clear delineation of the stopping criteria related to potential

harm occurring in each of the experimental groups and the justification for these stopping criteria.

(2) Regarding the informed consent document approved by the DUHS IRB, OHRP makes the following determinations:

(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, a description of the procedures to be followed, and identification of any procedures which are experimental.

(i) OHRP finds that the informed consent document failed to adequately describe the purpose of the research. In addition to simply stating that the purpose of the study was to compare two ways of inflating a patient's lungs, it would have been appropriate to include a statement that the main purpose of the study was to find out if patients with ALI and ARDS have a higher or lower death rate (or survival rate) when lungs are inflated with a low tidal volume (6 ml/kg PBW) versus a high tidal volume (12 ml/kg PBW).

In addition, it would have been useful to state that one reason for conducting the study was to determine what factors should be given priority when making clinical decisions related to setting the tidal volume in patients with ALI and ARDS.

(ii) OHRP finds that the informed consent document failed to adequately describe the nature of the experimental design. Additional information should have been included about the differences between the two research interventions and ventilator management that would have been provided as part of concurrent routine clinical practice outside the research context, particularly with respect to the upper limits of plateau pressure for each experimental group.

(iii) OHRP finds that the informed consent document failed to adequately describe the duration of the study. In particular, the study involved collection of subjects' identifiable private information for up to 180 days after enrollment, whereas the informed consent document 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 finds that the informed consent document failed to include death as one of the risks of the research. In particular, there was no statement that the subject could have a higher risk of death depending on which of the experimental groups he or she was assigned to, in comparison to the other experimental groups and in comparison to not entering the trial and thereby receiving individualized care based upon the best clinical judgement of the subject's physicians.

(c) HHS regulations at 45 CFR 46.116(a)(4) require that when seeking informed consent, a description of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject shall be provided to the subject or the subject's legally authorized representative.

OHRP finds that the informed consent document failed to include an adequate description of alternatives to participating in the trial. In particular, it would have been appropriate to explain to prospective subjects or their legally authorized representatives that in consultation with their physicians, they could have chosen to receive a high tidal volume, a low tidal volume, or an intermediate tidal volume instead of participating in the research.

OHRP Findings Regarding the FACTT Trial

(3) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations, the IRB 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. In order for the IRB to make these required determinations, the IRB necessarily must be able to identify and assess accurately the risks to participating subjects.

(a) In its October 7, 2002 letter regarding the ARDS Network clinical trials, OHRP presented the concern that the FACTT trial failed to satisfy the requirements of 45 CFR 46.111(a)(1) and (2) because the trial (i) included two experimental groups (defined by low target levels of central venous pressure [CVP] or pulmonary artery occlusion pressure [PAOP] in the "fluid conservative" experimental group and high target levels of CVP or PAOP in the "fluid liberal" experimental group); (ii) lacked a "routine care"

control group managed with either individualized target CVPs and PAOPs based upon physician clinical judgement or target CVPs and 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 in patients with ALI and ARDS during routine clinical practice at the time the study was initiated; and (iii) as a result of (i) and (ii), lacked an adequate plan to monitor for harm to subjects in each experimental study group (i.e., a potentially increased mortality rate in comparison to not participating in the research).

With regard to whether the design of the FACTT trial actually failed to minimize risks to subjects or whether the risks of participation in the trial actually were unreasonable in relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result, almost all of the consultants engaged by OHRP opined that risks to subjects participating in the FACTT trial were minimized and reasonable in relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result. OHRP believes, however, that the interests of future human subjects would be served best by further discussion within the scientific and bioethics communities about issues regarding appropriate research design in the absence of a standard of care that have been raised in the context of OHRP's compliance oversight evaluation of the FACTT trial. OHRP encourages such discussions. Furthermore, as noted below, OHRP finds that the DUHS IRB responsible for oversight of the FACTT trial will need to receive additional information from the ARDS Network investigators and re-assess whether the FACTT trial as designed satisfies the requirements of the HHS regulations at 45 CFR 46.111(a)(1) and (2).

(b) OHRP finds that when reviewing and approving the FACTT trial, the DUHS IRB failed to receive or request sufficient information to make the determinations required under 45 CFR 46.111(a)(1) and (2).

In particular, OHRP finds that in order to have determined whether the risks to the subjects were minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably have been expected to result, the DUHS IRB should have received information adequate to assess the risks and potential benefits of each of the interventions for each arm of the FACTT trial relative to concurrent routine clinical practice outside the research context. OHRP further finds that at least the following additional information would have been needed to make these determinations:

(i) A clear, detailed description of concurrent routine clinical practice at the ARDS Network trial sites with respect to management of intravascular fluid

status and target CVPs and PAOPs in patients with ALI and ARDS, including the various clinical factors that effect clinical decision making related to the selection of target CVPs and PAOPs. OHRP suggests that, ideally, this description would have included a frequency distribution of targeted and actual levels of CVP and PAOP in patients with ALI and ARDS over the course of their illness in routine practice at the institutions where the FACTT study was to be conducted.

(ii) A description of the mean and standard deviation of normal (i.e., euvolemic) levels of CVP and PAOP.

(iii) A more detailed explanation of the basis for selecting the two experimental fluid management strategies that were to be used and a detailed comparison of these strategies relative to concurrent routine clinical practice.

(iv) A clear statement of the target levels of CVP and PAOP for each experimental group.

(v) A more detailed description of the data and safety monitoring plan for the trial, including a clear delineation of the stopping criteria related to potential harm occurring in either of the experimental fluid management groups and the justification for these stopping criteria.

(4) Regarding the informed consent document approved by the DUHS IRB, OHRP makes the following determinations:

(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, a description of the procedures to be followed, and identification of any procedures which are experimental.

(i) OHRP finds that the informed consent document failed to adequately describe the purpose of the research. In addition to simply stating that the purpose of the study was to compare the effectiveness of two different catheters and two different ways of managing fluids, it would have been appropriate to include the statement that the main purpose of the study was to find out if patients with ALI and ARDS have a higher or lower death rate (or survival 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. In addition, it would have been useful to state that one reason for conducting the study was to determine what factors should be given priority when making clinical decisions related to management of fluid balance in patients with ALI and ARDS.

(ii) OHRP finds that the informed consent document failed to adequately describe the nature of the experimental design, the two experimental fluid management strategies, and the differences between the experimental fluid management interventions and fluid management that would have been provided as part of concurrent routine clinical practice outside the research context. Furthermore, OHRP finds that the characterization of the two fluid management strategies being compared in the study as being "considered part of standard care" may have been misleading and inaccurate given the following description of these strategies in the FACTT protocol:

> "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]

In addition, OHRP acknowledges the following statement on page 66 of the March 12, 2003 ARDS Network Investigators' Response to the October 7, 2002 OHRP letter:

> "Regarding '*Both types of [fluid management] methods are considered standard of care'*, we agree that this phrase is suboptimal. While the specific interventions in the management strategies are considered standard of care, the actual strategies themselves are experimental."

(iii) OHRP finds that the informed consent document failed to describe the

differences between the two experimental fluid management strategies with respect to diuretic dosing and dobutamine dosing. Instead, the informed consent document implied that the only difference between the fluid conservative management and fluid liberal management was the amount of fluid administered.

(iv) OHRP finds that the informed consent document failed to indicate that the subject would be required to be placed on a tidal volume of 6 ml/kg PBW if he or she was not being treated with such a tidal volume prior to enrollment.

(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.

(i) OHRP finds that the informed consent document failed to include death as one of the risks of the fluid management strategies used in the research. In particular, the informed consent document did not include a statement that the subject could have a higher risk of death depending on which of the experimental groups he or she was assigned to, in comparison to each of the other experimental groups and in comparison to not entering the trial and instead receiving individualized care based upon best clinical judgement of the subject's physicians.

(ii) OHRP finds that the informed consent document failed to include a description of any risks associated with having the tidal volume lowered to 6 ml/kg PBW for those subjects who may have been on a higher tidal volume prior to enrollment in the research. These risks may have included increased probability of developing hypercapnia, respiratory acidosis (requiring more sodium bicarbonate), and agitation and dyspnea (requiring greater sedation).

(iii) OHRP finds that the informed consent document failed to describe the risks associated with each of the experimental fluid management strategies. For example, there was no mention in the informed consent document that subjects assigned to the fluid conservative management group might experience inadequate organ perfusion which could result in renal failure, ischemic brain injury, cardiac ischemia, or other end organ damage. Likewise, there was no mention in the informed consent document that subjects assigned to the fluid liberal group could experience excessive pulmonary edema and delayed lung recovery. Furthermore, depending on study group assignment, subjects could have received higher doses of diuretics and dobutamine than they would have received if they had not entered the clinical trial, yet in the informed consent

document there was no discussion of the risks of receiving higher or more frequent doses of these drugs.

(c) HHS regulations at 45 CFR 46.116(a)(4) require that when seeking informed consent, a description of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject shall be provided to the subject or the subject's legally authorized representative.

OHRP finds that the informed consent document failed to include an adequate description of alternatives to participating in the trial. In particular, it would have been appropriate to explain to prospective subjects or their legally authorized representatives that in consultation with their physicians, they could have chosen to receive the liberal fluid management strategy, the conservative fluid management strategy, or an intermediate fluid management strategy instead of participating in the research.

(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 finds that, in general, the language throughout most of the informed consent document would not have been understandable to most subjects or their representatives. In particular, the descriptions of the research interventions, the alternatives, and the risks and discomforts in general were confusing and difficult to understand.

Required Actions

(1) If DUHS intends to resume enrollment of subjects in the FACTT trial, it must ensure that an IRB designated under DUHS's OHRP-approved assurance receives and reviews the following:

(a) Additional supplemental information from the ARDS Network investigators sufficient for the IRB to make the determinations required under HHS regulations at 45 CFR 46.111(a)(1) and (2). This supplemental information should address the items listed in findings (3)(b)(i)-(v) above.

(b) A revised proposed model informed consent document that addresses findings (4)(a)-(d) above. OHRP acknowledges that the ARDS Network investigators agreed that the informed consent documents for the FACTT trial could be better and indicated a willingness to make revisions to these documents.

If the DUHS IRB receives and reviews the information and documents in (a) and (b) above and subsequently re-approves the research, the National Heart, Lung, and Blood Institute (NHLBI)

could then rescind its suspension of enrollment of new subjects into the FACTT trial at DUHS.

(2) If the DUHS IRB re-approves the FACTT trial, DUHS must provide OHRP with a copy of the final version of the IRB-approved informed consent document.

(3) In light of the issues raised in this review DUHS must complete a re-assessment of its processes and procedures to ensure that the IRBs designated under DUHS's OHRP-approved assurance (a) receives sufficient information to make all determinations required under HHS regulations at 45 CFR 46.111; and (b) approves an informed consent process that satisfies all requirements of HHS regulations at 45 CFR 46.116. Upon completion of the reassessment, appropriate actions shall be taken, and a report describing these actions should be submitted by DUHS to OHRP by August 29, 2003.

OHRP is available to assist DUHS in implementing the required actions described above.

Additional OHRP Comments and Guidance

(1) HHS regulations at 45 CFR 46.107(a) state, among other things, that an IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

In accordance with these regulatory requirements, an IRB should have members who can assess the scientific design of the research being proposed and the acceptability of the proposed research interventions in comparison to concurrent routine clinical practice. Furthermore, in accordance with HHS regulations at 45 CFR 46.107(f), when an IRB lacks necessary expertise relevant to the review of a particular research project, the IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB, but their attendance at an IRB meeting must be recorded in the minutes of the IRB meeting.

(2) As previously noted above, HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research covered by the regulations, the IRB 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.

In order for the IRB to make the determinations required under HHS regulations at 45 CFR 46.111(a)(1) and (2), as well as most of the other determinations required under 45 CFR 46.111, the IRB must receive and thoroughly evaluate sufficient information describing the research design. Ensuring that sufficient information is received and reviewed by the IRB is a shared responsibility of both the investigators proposing the research and the reviewing IRB. The ability of the IRB to recognize that sufficient information has been submitted to the IRB by the investigators requires IRB members with appropriate relevant professional experience, competence, and expertise.

Furthermore, making the determinations required under HHS regulations at 45 CFR 46.111 cannot be deferred or delegated by the responsible IRB designated under an OHRP-approved assurance to any other committee or body.

(3) In reviewing the ARDS Network trials, OHRP noted the following: (i) ALI and ARDS are rapidly progressive disorders with high short-term mortality rates; (ii) the prospective subjects for these trials were in nearly all cases not expected to be able to consent on their own behalf; (iii) given their medical condition and impaired capacity to consent, the prospective subjects likely were highly vulnerable; (iv) the primary study endpoint was short-term mortality; and (v) subjects in each experimental group of the ARMA and FACTT trials potentially may have been disadvantaged compared to patients treated according to concurrent routine clinical practice. Given these observations about the ARDS Network trials, it is incumbent upon the ARDS Network investigators to provide in their written protocols a more expansive, substantive discussion of the multiple complex ethical and regulatory issues related to the protection of human subjects that must be addressed by the IRBs reviewing such research.

For instance, OHRP recommends that ARDS Network written protocols include a more detailed, substantive discussion of the following issues, among others:

> (a) The reasonably foreseeable risks to the subjects and whether these risks are reasonable for the prospective subject population in relation to anticipated benefits, if any, to the subjects and the importance of knowledge that may reasonably be expected to result.
>
> (b) The specific procedures that will be implemented in the study design to minimize risks to subjects and an explanation as to why these procedures are adequate.
>
> (c) The provisions for monitoring the data to ensure the safety of subjects in all study groups and an explanation as to why these provisions are adequate.

(d) 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.

(e) The additional safeguards that will be included for subjects who are likely to be vulnerable to coercion or undue influence (e.g., independent consent monitors might be considered).

(f) For subjects for whom consent would be initially obtained from a legally authorized representative, 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.

(g) An explanation as to whether the research satisfies the requirements under HHS regulations at 45 CFR part 46, subpart D, for trials proposing to involve children.

(h) The basis for excluding pregnant women from the trials.

OHRP acknowledges that the ARDS Network investigators have already begun to take steps to address some of these complex ethical issues in their clinical trials.

(4) With respect to the ARMA study, since the risks to subjects likely may have varied incrementally depending upon the change in tidal volume and plateau pressure relative to baseline that subjects would have experienced upon randomization, OHRP suggests that it may have been appropriate for the informed consent process to include a procedure for communicating the incremental nature of the risk to subjects based upon their known baseline tidal volume and plateau pressure prior to enrollment in the research (OHRP acknowledges that a similar procedure for communicating the incremental nature for potential benefits also may have been appropriate).

OHRP appreciates the commitment of DUHS to the protection of human subjects. Do not hesitate to contact us should you have any questions.

Sincerely,

Kristina Borror, Ph.D.
Director
Division of Compliance Oversight

Michael A. Carome, M.D.
Associate Director for Regulatory Affairs
Office for Human Research Protections

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