How Best to Ventilate?

Trial Design and Patient Safety in Studies of the Acute Respiratory Distress Syndrome

Robert Steinbrook, M.D.

Each year, about 150,000 people in the United States have acute lung injury or its most severe form, the acute respiratory distress syndrome — devastating lung diseases associated with a mortality rate of between 30 and 50 percent. Despite the severe lung injury, pulmonary function in most survivors returns nearly to normal within 6 to 12 months. Unfortunately, the search for effective treatments to keep patients alive while their lungs heal has lagged behind the substantial progress in basic research. Almost all the treatments that have been tested in clinical trials have not worked.1,2 After years of bad news, the National Heart, Lung, and Blood Institute (NHLBI) announced in March 1999 that it had stopped a multicenter clinical trial, conducted by the Acute Respiratory Distress Syndrome (ARDS) Network, of the use of mechanical ventilation in patients with the acute respiratory distress syndrome because the group receiving a lower tidal volume than had traditionally been used had substantially fewer deaths than the group receiving a larger tidal volume. “This is the first large clinical trial to demonstrate a more effective treatment for ARDS patients,” stated Dr. Claude Lenfant, the director of the institute. “The findings will improve the care of these patients and save thousands of lives each year.”3 Recently, Dr. Thomas R. Martin of the University of Washington, the president of the American Thoracic Society, called the trial “a landmark study that was the single most important contribution to the care of patients with ARDS since the syndrome was first described in 1967 by Ashbaugh and Petty.”4

The study was sponsored by the NHLBI and published in the Journal.3 During the past year, however, it has become the focus of an ongoing controversy about study design and patient safety. In July 2002, the institute stopped enrollment of patients in another large ARDS Network study, a comparison of different approaches to the use of intravenous fluids and catheters.6 The institute then reviewed the two disputed clinical trials and gave them a clean bill of health.7 Nonetheless, these studies are under investigation by the Office for Human Research Protections (OHRP), the office in the Department of Health and Human Services that regulates institutions and other entities that conduct or oversee studies involving human subjects (Table 1).10 The investigation involves many of the nation’s leading academic medical centers and critical care physicians.

Concern voiced by two physicians in the department of critical care medicine at the National Institutes of Health (NIH) Clinical Center triggered the controversy and the investigation by the OHRP.11 Drs. Peter Q. Eichacker and Charles Natanson, both senior investigators in the department, contend that the study of tidal volumes did not use a control group that reflected “the current best practice standards of the time.” Thus, they argue, participants were subjected to unnecessary risks, the researchers could have erroneously concluded that the use of lower tidal volumes can save lives, and “further clinical trials are necessary to determine whether lowered tidal volumes produce a survival benefit when compared with the intermediate tidal volumes . . . routinely used by participating physicians at the time.” They have raised similar questions about the design of the study of intravenous fluids and catheters.

Dr. Gordon R. Bernard of Vanderbilt University, the chair of the steering committee of the ARDS Network, said that the investigators “remain very satisfied that we are performing the highest-quality studies and that patient safety is not compromised.” In an interview, he added, “We really believe in our hearts that the questions we are asking have implications for the life and death of a lot of critically ill patients around the world. This is not simply an issue of patient safety in the current studies,
but (an issue regarding) the way medicine is currently practiced and will continue to be practiced in the absence of the data we are seeking." In this article, I discuss the controversy about trial design and patient safety in the ARDS Network studies and the implications of this controversy.

### Background

In preparing this report, I spoke in detail to more than a dozen people with extensive knowledge of the controversy and various points of view. Contentious debates about the design of clinical studies and the interpretation of the findings are often resolved after a review by independent experts, further analysis of data, additional studies, or a combination of these approaches. In the case of the ARDS Network studies, the involvement of the OHRP and the suspension of an active trial have focused attention on the safety of the research subjects as well as the design of the studies.

Regulations of the Department of Health and Human Services set criteria for the approval of research by institutional review boards (IRBs). The regulations require that the risks to research subjects be minimized “by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.”

---

**Table 1. Studies of the Acute Respiratory Distress Syndrome That Are under Review by the OHRP.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDSNet Study 01, Respiratory Management in Acute Lung Injury and the Acute Respiratory Distress Syndrome (ARMA)</td>
<td>A comparison of positive pressure ventilation with an initial tidal volume of 12 ml/kg of predicted body weight (with plateau pressures limited to 50 cm of water) vs. a tidal volume of 6 ml/kg (with plateau pressures limited to 30 cm of water) for treatment of acute lung injury and the acute respiratory distress syndrome. Conducted between March 1996 and March 1999 at 10 academic medical centers and affiliated hospitals; conducted simultaneously with two other studies. Stopped in March 1999 after 861 patients had been enrolled because the use of the lower tidal volume was found to decrease mortality. Report published in May 2000.</td>
</tr>
<tr>
<td>ARDSNet Study 05, Fluid and Catheters Treatment Trial (FACCT)</td>
<td>A comparison of the use of a pulmonary-artery catheter with the use of a central venous catheter for management of acute lung injury and the acute respiratory distress syndrome and a comparison of conservative and liberal fluid-management strategies; a 2x2 factorial design used to combine the studies. Protocol stipulated all subjects to be initially ventilated with a low tidal volume (6 ml/kg). Patients enrolled beginning in July 2000; conducted at 19 university centers and affiliated hospitals. Suspended by the NHLBI at the request of the OHRP on July 25, 2002, after 418 patients had been enrolled; still suspended as of March 2003. Planned enrollment is a maximum of 1000 patients.</td>
</tr>
<tr>
<td>ARDSNet Study 04, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury (ALVEOLI)</td>
<td>A comparison of two ventilation strategies for patients with acute lung injury and the acute respiratory distress syndrome — higher positive end-expiratory pressure with a lower fraction of inspired oxygen and lower end-expiratory pressure with a higher fraction of inspired oxygen. Protocol stipulated all subjects to be initially ventilated with a low tidal volume (6 ml/kg). Conducted between November 1999 and February 2002; enrolled 550 patients. Stopped for “lack of efficacy”. Report not published as of March 2003. Review by the OHRP deferred until the other trials are reviewed.</td>
</tr>
</tbody>
</table>

also require that the “risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects” and in relation to the importance of the knowledge that may be gained. According to the OHRP, meeting “the highest ethical standards and regulatory requirements” was of “paramount importance” in the ARDS Network studies, because the subjects had a disorder that may rapidly become lethal, the subjects were, in nearly all cases, unable to provide consent on their own behalf, and the primary study end point was short-term mortality.

For these studies, the central design issue was the choice of comparison groups. Did both the tidal-volume trial and the fluid-and-catheters trial evaluate two extremes of practice rather than examining the ways in which cases were most commonly managed, which may be safer? Or has the care of patients with the acute respiratory distress syndrome been so highly variable that there really has been no standard, even if some procedures for ventilation or approaches to fluid management have been used more commonly than others? Were the choices of comparison groups at least as reasonable as any other choices that might have been made?

“It is a valid question, how best to design these studies. No one size fits all,” Bernard said. He added, “This is a disagreement about study design. We think it is a study-design issue, not an ethical issue.” Eichacker, however, has a different view. “There is a safety issue and certainly an issue about the safety of patients participating in research,” he said in an interview. “It is a design issue but with a safety component. In the end, do you know what the safety is of the treatment that is shown to be best if that treatment has not been compared to what physicians deemed best at the time of the study?”

THE TIDAL-VOLUME STUDY

The NHLBI established the ARDS Network in 1994 for the conduct of clinical trials. It now comprises 20 academic medical centers in the United States and Canada (Table 2). So far, the total amount that has been spent for the network and its trials is $37.4 million.

Soon after the network was created, the investigators designed a study to compare ventilation at lower tidal volumes with ventilation at higher tidal volumes. Patients with the acute respiratory distress syndrome have severe damage to their alveoli, so they require supplemental oxygen and assisted ventilation. Yet mechanical ventilation can cause further injury, such as alveolar rupture and alveolar hemorrhage, particularly when high airway pressures stretch the lung excessively. If ventilation is too gentle, there may be hypoxemia, and respiratory acidosis may develop. Patients may then be uncomfortable and require neuromuscular blockade or sedation. Studies in animals and preliminary clinical studies had suggested that the use of a lower tidal volume might save lives — but the findings were conflicting.

When at rest, normal subjects have tidal volumes of 7 to 8 ml per kilogram of body weight. The ARDS Network study defined traditional approaches to mechanical ventilation for patients with the acute respiratory distress syndrome as those that used tidal volumes of 10 to 15 ml per kilogram. The trial compared an initial tidal volume of 12 ml per kilogram of predicted body weight (with plateau pressures limited to 50 cm of water) with an initial tidal volume of 6 ml per kilogram of predicted body weight (with plateau pressures limited to 30 cm of water). The plateau pressures reflect the maximal pressures in the respiratory system during mechanical ventilation. Like other network studies, the study was reviewed and revised on the basis of the input of a protocol-review committee and a data and safety monitoring board and was approved by the IRBs at all the study sites. The data and safety monitoring board continued its work throughout the study.

The tidal-volume study began in March 1996. It was stopped three years later, after 861 of a planned 1000 patients had been enrolled. At the time of randomization, the tidal volumes of the subjects varied widely; the mean tidal volume among patients for whom data on tidal volume were available was 10.3 ml per kilogram of predicted body weight. Mortality was significantly lower in the 6-ml-per-kilogram group (31.0 percent) than in the 12-ml-per-kilogram group (39.8 percent) — a reduction of 22 percent. The mortality rate in the group with the lower tidal volume was low in comparison to that reported in other large groups of patients with the syndrome. The mortality rate in the group with the traditional tidal volume was similar to that in other large studies. The investigators interpreted their findings as demonstrating the potential harm caused by excessive stretching of the lungs during adjustments to mechanical ventilation. They concluded that “this lower-tidal-volume protocol should be used in patients with acute lung injury and the acute respiratory distress syndrome.”
After the tidal-volume study was completed, the ARDS Network began to enroll patients in two related studies (Table 1). One study, a comparison between ventilation with a higher level of positive end-expiratory pressure and ventilation with a lower level of pressure, began enrolling patients in November 1999 and was closed in February 2002. The other, a comparison of the use of a pulmonary-artery catheter with the use of a central venous catheter and a comparison of a “conservative” fluid-management strategy with a “liberal” fluid-management strategy, began enrolling patients in July 2000. Both studies used the 6-mg-per-kilogram protocol for tidal volume. The fluid-and-catheters trial was designed in response to the recommendations of a joint workshop of the NHLBI and the Food and Drug Administration. The best approach to fluid management has been a “huge controversy over the years,” said Dr. Herbert P. Wiedemann of the Cleveland Clinic Foundation, the chair of the study. “We have been flying blind. There is the potential for a huge impact on mortality.”

**Table 2. The Acute Respiratory Distress Syndrome (ARDS) Network.**

<table>
<thead>
<tr>
<th>Clinical coordinating center:</th>
<th>Massachusetts General Hospital, Boston</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical centers:</td>
<td>Harborview Medical Center, Seattle</td>
</tr>
<tr>
<td></td>
<td>University of Michigan Medical Center, Ann Arbor</td>
</tr>
<tr>
<td></td>
<td>University of Maryland at Baltimore, Baltimore</td>
</tr>
<tr>
<td></td>
<td>Cleveland Clinic Foundation, Cleveland</td>
</tr>
<tr>
<td></td>
<td>University of Colorado Health Sciences Center, Denver</td>
</tr>
<tr>
<td></td>
<td>Duke University Medical Center, Durham, N.C.</td>
</tr>
<tr>
<td></td>
<td>Vanderbilt University Medical Center, Nashville</td>
</tr>
<tr>
<td></td>
<td>Hospital of the University of Pennsylvania, Philadelphia</td>
</tr>
<tr>
<td></td>
<td>LDS Hospital, Salt Lake City</td>
</tr>
<tr>
<td></td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td></td>
<td>Baylor College of Medicine–Ben Taub General Hospital, Houston</td>
</tr>
<tr>
<td></td>
<td>Baystate Medical Center, Springfield, Mass.</td>
</tr>
<tr>
<td></td>
<td>Louisiana State University Health Sciences Center, New Orleans</td>
</tr>
<tr>
<td></td>
<td>St. Paul’s Hospital, Vancouver, B.C., Canada</td>
</tr>
<tr>
<td></td>
<td>University of Chicago Medical Center, Chicago</td>
</tr>
<tr>
<td></td>
<td>University of Texas Health Science Center, San Antonio</td>
</tr>
<tr>
<td></td>
<td>University of Virginia Health Systems, Charlottesville</td>
</tr>
<tr>
<td></td>
<td>University of Pittsburgh Medical Center, Pittsburgh</td>
</tr>
<tr>
<td></td>
<td>Wake Forest University Baptist Medical Center, Winston-Salem, N.C.</td>
</tr>
</tbody>
</table>

* Information is from ARDSNet (http://hedwig.mgh.harvard.edu/ardsnet/contact.html).

**CONCERN ABOUT INFORMED CONSENT**

In the summer of 2000, the OHRP first became involved with the tidal-volume study. After receiving a complaint about the informed-consent procedures, the office evaluated the 12 major sites. Because nearly all the subjects were too ill to provide consent themselves, informed consent had to be obtained from other persons on their behalf. In all cases, the office found that the informed-consent documents approved by the IRBs for the research “failed to describe adequately the reasonably foreseeable risks and discomforts.” It also found some instances in which subjects had been enrolled even though legally effective informed consent had not been obtained. In most instances, howev-
er, the office found that the institutions “presented a reasonable basis under applicable state law” for their interpretation that individuals who consented on behalf of the subjects were legally authorized to do so. In response, the institutions took various corrective actions. In some states, procedures for surrogate consent for participation in research were clarified by enacting new laws, as in California, or by seeking to revise state health care regulations, as in Tennessee. This evaluation has essentially been completed.

---

**Concerns about Study Design and Patient Safety**

Eichacker and Natanson, the physicians who raised questions about the ARDS Network studies, are senior investigators at the NIH Clinical Center. They care for patients from the institutes who require critical care services. They are not part of the NHLBI.

In an interview, Eichacker said that they became concerned after they read the reports of the tidal-volume study and learned about the design of the fluid-and-catheters trial. Their concern increased as they prepared an analysis of five studies testing low tidal volumes, including the ARDS Network study. They concluded that the best explanation for the contradictory findings in the five trials was that “both high and low tidal volumes and airway pressures may be associated with increased mortality rate compared with common clinical practice.”

The analysis was published in the American Journal of Respiratory and Critical Care Medicine in December 2002, along with a response from the ARDS Network and an editorial by Dr. Thomas E. Stewart of the University of Toronto that lauded the tidal-volume study. They concluded that the best explanation for the contradictory findings in the five trials was that “both high and low tidal volumes and airway pressures may be associated with increased mortality rate compared with common clinical practice.”

According to Dr. Roy G. Brower of Johns Hopkins University, the chair of the tidal-volume study, there were “numerous reasons we believed that participating in this study would be safe, not risky.” In an interview, Brower said that although the tidal volume of 12 ml per kilogram of predicted body weight used in the traditional-tidal-volume group was greater than the mean tidal volume of 10.3 ml per kilogram at randomization, the use of this volume was “not very different from mainstream clinical practice. We used tidal volumes that were mainstream [in terms of] current practice and contemporary opinion.” The study excluded patients who could be harmed by the protocol, such as those with increased intracranial pressure or severe chronic respiratory disease. The detailed protocol and training of the staff should also have decreased the risk. “There is a substantial body of evidence that when intensive-care-unit staff use protocols, it improves patient care,” he said.

---

**The Response by the NHLBI**

In November 2001, Eichacker and Natanson and two statisticians sent a letter of concern about patient safety and a copy of their manuscript to an official at the NHLBI who worked with the ARDS Network. “We sent a letter via express mail,” Eichacker said. “We were never given a response.” The letter stated in part, “We believe [the ongoing ARDS Network] trials should be altered immediately to incorporate a standard practice control.”

According to Diane Striar, a spokeswoman for the NHLBI, the material from Dr. Eichacker and his colleagues was received on November 13. The manuscript was labeled confidential. Although the NHLBI did not respond to Eichacker, “we carefully evaluated the material he sent to us and discussed it with several ARDS Network investigators and the coordinating center,” Striar said. “Our review did not support Eichacker’s claims. Because the material was sent to us as a confidential communication, we did not share it with external consultants or the ARDS Network steering committee.” She added that the institute “had no indication from any reporting of adverse events or routine [reviews by the data and safety monitoring board] of the data that any patients were placed at increased risk.”

On July 17, 2002, Eichacker and Natanson met with Dr. Greg Koski, the director of the OHRP. They described their concerns and gave him a copy of their manuscript. (Later in 2002, Koski left the government to return to Massachusetts General Hospital; he did not participate in the investigation, because the clinical coordinating center of the ARDS Network is at his institution.) Separately,
on July 29, the Alliance for Human Research Protection, a patient-advocacy group based in New York City, sent a letter of complaint to the office.30 The letter raised an additional issue — that the tidal-volume study should have been stopped earlier, given the large difference in mortality between the two treatment groups.

On July 25, following discussions with the OHRP, the NHLBI put the fluid-and-catheters trial on hold.7 When the study was suspended, 418 of a projected 1000 patients had been enrolled. The institute then asked five external consultants to review the studies. The consultants were chosen with input from the ARDS Network, Eichacker and Natanson, and the OHRP. The ARDS Network investigators also prepared a detailed response.

On August 30, the institute convened a closed meeting of the consultants and all the key parties to discuss the issues. According to Lenfant, the expert panel “unanimously stated that the [fluid-and-catheters] study was well designed, safe and likely to result in important results for ARDS patients.”7 Although the instituteconcurred with the panel’s recommendation that the trial be resumed, it continued the “voluntary clinical hold.”7

“It is kind of a paradoxical situation,” Lenfant said in an interview in February. “The decision to suspend the trial is from the National Institutes of Health, from this institute. And in view of all that we have said, we do not believe that there is reason for doing so. [The trial] should be reinstated. That is what we intend to argue with the Office for Human Research Protections.”

Eichacker said that his involvement with the evaluation, as well as that of Natanson, ended with the August 30 meeting. “We have had limited communication with the Office for Human Research Protections since then. We were asked to come in and present the question, and that was that.”

The members of the expert panel were Dr. Deborah J. Cook of McMaster University in Canada, Dr. John E. Heffner of the Medical University of South Carolina, Dr. Mitchell M. Levy of Brown University, who chaired the panel, Wasima N. Rida of the Food and Drug Administration, and Dr. Robert D. Truog of Harvard Medical School. According to Lenfant, they were asked to make their recommendations “individually, rather than collectively.” Their written comments ranged from 2 to 12 pages, according to copies that were made available to me.

Cook urged that the “ARDSNet investigators proceed with their landmark, world class investigations.” Heffner criticized the analysis published by Eichacker and his colleagues11 and concluded that both the tidal-volume and fluid-and-catheter studies were “appropriately designed.” Levy said that he did not believe the concerns to be valid and that the fluid-and-catheters trial was “safe” for both experimental groups. “The logic for almost every issue is based on the assertion that there is, or could be, an identifiable ‘current standard of care’ or ‘routine care’ for either mechanical ventilation in ARDS or fluid management. The literature is fraught with debate and controversy about the standard of care for both of these treatment modalities. . . . It is this ongoing variation that lends such importance to both the . . . trials.”

Rida said that it was “reasonable and appropriate” to use a tidal volume of 6 ml per kilogram as the “standard ventilation practice” in the fluid-and-catheters trials. Although the addition of a group with “intermediate” fluid management would be “scientifically useful,” Rida concluded that “it is ethical to permit the ARDS Network investigators to resume enrollment . . . as the protocol currently stands.” Finally, Truog found that the tidal-volume study was “ethical, did not expose subjects to avoidable risk, and yielded very valuable information.” The design of the fluid-and-catheters study was “ethical,” the liberal and conservative approaches to fluid management were “well within the range of existing practices,” and the protocol was “well-designed to show whether fluid management makes a difference in outcome” in patients with the acute respiratory distress syndrome.

The Investigation by the OHRP

On October 7, 2002, the OHRP sent a 29-page letter to officials at three leading ARDS Network institutions.10 Dr. Michael A. Carome, who is currently the office’s associate director for regulatory affairs, wrote that the office “continues to have serious unresolved concerns” about the possibility that three trials “failed to comply with key requirements of the Department of Health and Human Services regulations for the protection of human subjects.” The office has subsequently deferred its review of the study of positive end-expiratory pressure (Table 1).

Carome raised questions about the control groups and the possibility that the subjects “may have been placed at an increased risk of death” as compared with the risk they would have incurred if
different groups had been used. One potential control group would be a group receiving tidal volumes that were the “standard of care”; patients in such a group would receive “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.” According to Brower, “standard” ventilation practices are “highly variable and impossible to characterize,” and “any comparisons of outcome from such a control group to a protocol group would have been almost entirely meaningless.”

Another potential control group would be one receiving “average” tidal volumes that were based on a “systematic assessment of routine clinical practice . . . at the time the study was conducted.” For the tidal-volume study, “this presumably would have been a tidal volume set somewhere between 7 and 11 ml per kilogram of predicted body weight.” For the fluid-and-catheters study, similar control groups would be a group receiving “individualized fluid management” according to the “standard of care” and a group receiving “average” fluid management that was based on a “systematic assessment of routine clinical practice” with regard to target central venous pressure or pulmonary-artery-occlusion pressure.

Carome asked for a detailed response, documents, and additional data. He requested extensive information about patients who were treated at the study institutions before the studies began who would have been eligible for the trials, those screened for the studies but not enrolled, and those who were enrolled. The OHRP “expects the clinical hold [on the fluid-and-catheters trial] to remain in effect” until the completion of the evaluation.

Although there are only limited data, it appears that more physicians in the United States are using lower tidal volumes to ventilate patients with the acute respiratory distress syndrome, but not necessarily a tidal volume as low as 6 ml per kilogram. A study from Minnesota showed that tidal volumes started to decline in mid-to-late 1998, before the ARDS Network study was completed. In the two years after the results were released, physicians prescribed mean ±SD tidal volumes of 10.1±1.9 ml per kilogram. A study from Harborview Medical Center in Seattle, an ARDS Network site, showed that publication of the study results had minimal effects on practice. From July 1999 to February 2001, less than about a quarter of patients with acute lung injury had tidal volumes of 6 ml per kilogram of predicted body weight or less at any time when the ventilator was checked. There is also clinical debate about the relative importance of limits on tidal volume and plateau pressure — in different patients, the same tidal volume (after adjustment for body weight) may result in different plateau pressures. “Rigid ideas about what tidal volumes are best are fraught with error, but it is what gets people exercised,” said Dr. John J. Marini of the University of Minnesota, an authority on mechanical ventilation who is not part of the ARDS Network. “All things being equal, a lower tidal volume is probably better than a very high tidal volume. But there are inherent problems in trying to apply general guidelines to specific patients with this syndrome.”

As of March 2003, the fluid-and-catheters trial remained on hold, and the investigation by the OHRP was continuing. It could take several months or longer to complete. Although this is not the office’s typical or usual case, issues of study design are within the scope of federal regulations for the protection of research subjects. OHRP plans to give a high priority to resolving the ARDS Network investigation in an expeditious fashion,” according to Dr. Bernard Schwetz, the acting director of the office.

The investigation and the suspension of a major NIH study have caused substantial and continuing dismay among many who are affected. For example, in January, Martin, the president of the American Thoracic Society, expressed the concerns of the society to Tommy Thompson, the Secretary of Health and Human Services. The OHRP “has chosen to set aside the findings of an expert panel convened by...
[the NHLBI] which included members approved in advance by OHRP,” Martin wrote. “This panel found that the allegations against the [ARDS Network investigators] were without scientific merit.” The ORHP, however, was not satisfied with the adequacy of the review by the panel convened by the NHLBI. It believes that a continued pause until the matter is sorted out is wise.

There are several ways in which the matter might be resolved. The OHRP could exonerate the ARDS Network studies, or it could decide that they were flawed and jeopardized the safety of the research subjects. If the office faults the design of the fluid-and-catheters study, the trial might have to be permanently stopped or continued with a substantially modified protocol. The long suspension has also raised practical questions about whether the trial can be restarted, regardless of the outcome of the investigation. “We had hoped that our analysis would raise sensitivities, that there might be a temporary hold, and an attempt would be made at a redesign,” Eichacker said. “We never wanted the ARDS Network not to do its trials or this trial. The questions are still important ones.”

Another approach would be for an independent group, such as a committee of the Institute of Medicine, to examine the entire controversy and its broader context and to make recommendations. Requiring many large clinical trials to include a control group in which patients receive either individualized care or care determined by systematic assessments of routine clinical practice would have far-reaching implications for trial design and for the assessment of potential risks to research subjects. The approach to trial design used by the ARDS Network is common in clinical research. For example, it has been used in studies of blood transfusion and many phase 3 trials of chemotherapeutic strategies. Thus, the outcome of the review could affect many other studies.

According to Lenfant, the current situation has no precedent. Lenfant said that since he became the director of the NHLBI in July 1982, “we have supported and conducted successfully a large number of clinical trials. I have never seen a situation like this one. . . . It is really a bizarre situation, and I think that is why we are a little mystified.”

8. ARDSNet. 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). Prospective, randomized multi-center trial of “fluid conservative” vs. “fluid liberal” management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). (Accessed March 14, 2003, at http://hedwig.mgh.harvard.edu/ardsnet/ards05.html.)