What Is the Legacy of the National Institutes of Health Acute Respiratory Distress Syndrome Network?

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It has been almost 15 years since the National Institutes of Health created the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDS Network) and nearly a decade since the completion of the landmark low-tidal volume (V_T) trial. In retrospect, the ARDS Network had a profound impact on the design and conduct of clinical trials in critical care. It represented the first time the federal government funded a clinical trials network devoted to Phase-III testing of important, non-pharmacologic therapies. Also the ARDS Network introduced factorial design into critical-care research, which allowed Phase-II testing of promising therapies. Other important contributions from the ARDS Network may not become apparent for many years. These include the ongoing mentoring of a new generation of critical-care researchers, as well as continued testing on an enormous store of biological samples that inevitably will advance our understanding of the pathogenesis of ARDS. Perhaps someday this may lead to another therapeutic breakthrough. Part of the ARDS Network's legacy surely will have been the opening of a dialog regarding the design of clinical trials in critical care, as well as a concerted effort to improve the protection of subjects enrolled into those trials. Finally, the respiratory care profession itself has benefited, owing both to its critical role in the successful implementation of complicated therapist-driven protocols and also to the ARDS Network's novel practice of utilizing respiratory therapists as clinical coordinators. This has raised the profile and enhanced the stature of the respiratory care profession. *Key words: acute respiratory distress syndrome, acute lung injury, ethics, evidence-based medicine, Office of Human Research Protection, mechanical ventilation, tidal volume.* [Respir Care 2009;54(7):912–924.

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Introduction

I'd like to begin this lecture by expressing my gratitude to the program committee of the American Association for Respiratory Care for the honor of presenting the 24th Philip Kittredge Memorial Lecture. I feel compelled to say a few words in honor of the man for whom this lecture series serves as a living memorial. Among the many important people who have contributed to the substance and integrity of the respiratory care profession, Phil Kittredge stood at the forefront. He was the editor in chief of our Journal for 25 years until his passing 12 years ago. His vision, constancy, and unwavering commitment to our profession are unparalleled. Without Phil Kittredge there would be no Journal, and there might be little scientific foundation for the practice of respiratory care. I am proud to pay honor to the man and to his legacy.

The topic of today's lecture concerns another legacy: that of the National Institutes of Health's National Heart, Lung and Blood Institute's (NHLBI) Acute Respiratory Distress Syndrome Clinical Trials Network (ARDS Network). March 2009 marks the 10th anniversary of the low-tidal-volume (V_T) ventilation trial's[1] completion. Coming 32 years after ARDS was first described,[2] the low-V_T study (hereafter referred to by its pseudo-acronym ARMA) has been the only major breakthrough in the treatment of ARDS, and therefore has been regarded as *the* landmark study.[3] With an annual estimated mortality of 70,000,[4] the 22% relative reduction in mortality reported by the ARMA study[1] offers a huge potential benefit to society.

However, not long after publication of this landmark study, the ARDS Network found itself embroiled in controversy that, sadly, lingers in the minds of many clinicians to this day.[5] Because of that controversy, I need to make the following statement. For over a decade I worked as a clinical coordinator for the ARDS Network at the University of California San Francisco before leaving in 2007. The opinions presented in this lecture are my own and not those of the ARDS Network, San Francisco General Hospital, nor the University of California, San Francisco.

I will begin this lecture with a brief history of the circumstances that led to the formation of the ARDS Network and describe some of the unique aspects of this organization, before describing the results of the major clinical trials and discussing the contributions of the ARDS Network that constitute what I believe are its legacy. Afterwards, I'll present my own views on the controversy surrounding ARDS Network, and the subsequent investigation by the Department of Health and Human Services' Office for Human Research Protections (OHRP). Table 1 provides a chronology of the ARDS Network.

From the mid-1970s to the late-1980s, evidence from several animal model studies demonstrated that sustained high-V_T mechanical ventilation induces lung injury.[6-8] In the mid-1970s some clinical studies strongly suggested that, contrary to the clinical impression of homogenous lung damage, the lungs of patients with ARDS behaved mechanically as though the injury was heterogeneous. In particular, the application of positive end-expiratory pressure (PEEP) simultaneously caused both lung recruitment and overdistention that was strongly influenced by the corresponding V_T size.[9-11]

In 1986 both Gattinoni et al[12] and Maunder et al[13] showed that many patients with ARDS and diffuse bilateral opacities on chest radiographs had chest tomograms revealing that substantial areas of the lung were normal. Subsequent computed tomography studies confirmed the implications of earlier mechanical studies: that in ARDS normally aerated lung tissue is simultaneously over-distended as collapsed tissue is recruited.[14,15] From this emanated the concept of "baby lung"[16] and the idea that in ARDS, the lung may not be so much stiff as it is small and vulnerable to over-distention. In 1990 Hickling et al[17] published an uncontrolled study that suggested that a low-V_T, pressure-limited strategy may improve survival in ARDS. By the middle of that decade, leaders in the field of critical care began advocating a new approach to mechanical ventilation, emphasizing a lung-protective strategy.[4,18,19]

Birth of a Clinical Trials Network

In 1992 several conferences were convened to discuss the study and management of ARDS. One conference, sponsored by the lung division of the NHLBI and the ARDS Foundation, focused on the current state of clinical trials in ARDS.[20] Among the issues discussed was the need to fund large, placebo-controlled trials to test promising new therapies, as well as the need to organize academic centers of excellence for the treatment of ARDS. In addition, mechanisms would need to be set in place for mentoring a new generation of clinical scientists to sustain that research. It was thought that the National Institutes of Health would need to play a crucial role in funding such an endeavor if there was to be any progress in lowering the 50% mortality rate associated with ARDS. At that time, the estimated 70,000 lives lost annually from ARDS far exceeded the mortality rate from breast cancer (45,000/year).[21]

In the spring and autumn of 1992, the American Thoracic Society and the European Society of Intensive Care Medicine held a series of meetings with the goal of reaching broad consensus on a definition for ARDS as well as establishing guidelines for the conduct and coordination of prospective clinical trials. These meetings produced the landmark American-European Consensus Conference Report and the new concept of acute lung injury (ALI).[4] Among their recommendations was the need for prospective randomized trials with a control group. In addition it was agreed that these studies should impose standardized protocols with clearly defined treatment boundaries to min-

Table 1. Important Events in the History of the Acute Respiratory Distress Syndrome Network

May - October 1992	Conferences sponsored by the NHLBI, American Thoracic Society, and European Society of Intensive Care Medicine discuss the need for large well-funded studies of ARDS.
1994	The NHLBI establishes the ARDS Clinical Trials Network.
March 1996	Enrollment into the first clinical trial (Ketoconazole and Respiratory Management of Acute Lung Injury [KARMA]) commences.
January 1997	The DSMB stops the ketaconazole portion of the KARMA study after the first interim analysis, for futility.
August 1997	Enrollment into the Late Steroid Rescue Study (LaSRS) commences.
February 1998	Study of lisofylline is added to the tidal-volume study (LARMA).
March 1999	The DSMB stops the tidal-volume portion of the study (ARMA) after the third interim analysis, for efficacy of low tidal volume.
June 1999	The DSMB stops the lisofylline portion of the LARMA study after the first interim analysis, for futility.
November 1999	Enrollment into the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI) study (higher vs lower PEEP) commences.
April 2000	Publication of the ketaconazole study in *The Journal of the American Medical Association*
June 2000	Publication of the ARMA study in *The New England Journal of Medicine* Enrollment into the Fluid and Catheter Treatment Trial (FACTT) commences.
August 2000	Complaint filed with the OHRP, focused on informed consent procedures. In response, OHRP sends letter of inquiry to University of California, San Francisco institutional review board, which is expanded to all ARDS Network sites.
November 2001	Eichacker and Natanson send a letter of concern to the NHLBI regarding patient safety concerns related to the ARMA trial design.
January 2002	Publication of the lisofylline study in *Critical Care Medicine*
March 2002	The DSMB stops the ALVEOLI study after the second interim analysis, for futility.
July 2002	Eichacker and Natanson present their concerns to the OHRP. A separate complaint is filed with OHRP by the Alliance for Human Research Protection. NHLBI voluntarily suspends the FACTT study at the request of the OHRP, pending investigation into issues of consent practices and study design.
August 2002	An external 5-member expert panel (including DJ Cook, JE Heffner, MM Levy, WN Rida and RD Troug), chosen with input from the ARDS Network, Eichacker and Natanson, and the OHRP, reviews study-design issues. The unanimous decision of the panel is that the studies in question are well-designed, safe, and likely to yield important results for the management of patients with ALI. The expert panel recommends the FACTT study resume.
October 2002	OHRP continues study suspension, citing its ongoing concerns regarding study design and patient safety. In a 29-page letter to the ARDS Network, the OHRP requests further documentation supporting the appropriateness of ARDS Network's study design.
December 2002	Publication of Eichacker et al critique of the ARMA trial in *The American Journal of Respiratory and Critical Care Medicine* Rebuttal by the ARDS Network, and editorial supporting the ARDS Network, by Martin, appear in the same issue.
July 2003	ARDS Network submits a 74-page response (including hundreds of pages of supporting data and documents) to the OHRP letter of October 2002. OHRP organizes an 8-member panel of experts in bioethics, human subjects protection, biostatistics, and pulmonary/critical-care medicine to review the ARDS Network submission. The expert panel finds the ARDS Network study designs minimize risks to the study subjects. OHRP lifts temporary hold on the FACTT study, and enrollment resumes.
November 2003	Enrollment completed into the LaSRS study
July 2004	Publication of the ALVEOLI study in *The New England Journal of Medicine*
October 2005	Enrollment into the FACTT study completed
April 2006	Publication of the LaSRS study in *The New England Journal of Medicine*
May 2006	Publication of the pulmonary arterial versus central venous catheter study in *The New England Journal of Medicine*
June 2006	Publication of the fluid-management study in *The New England Journal of Medicine*
November 2006	Enrollment into the Trophic Enteral Feedings versus Early Advancement to Full Caloric Enteral Feedings and Anti-Oxidant Supplement (EDEN-OMEGA) study commences.
August 2007	Enrollment into the Albuterol for the Treatment of ALI (ALTA) trial commences.
September 2008	The DSMB stops the ALTA study after the first interim analysis, for futility.

NHLBI = National Heart, Lung, and Blood Institute
ARDS = acute respiratory distress syndrome
DSMB = data safety management board
ALI = acute lung injury
OHRP = Office for Human Research Protections

imize variability in management. To do otherwise, in their opinion, would greatly impair the ability to draw unambiguous conclusions from study results.

In 1994 the NHLBI established the ARDS Network as a contract program. What was novel about the ARDS Network was that the NHLBI charged it with designing and conducting studies specifically aimed at improving clinical outcomes. Ten sites from across the United States were chosen, following a national competition. The first task before the ARDS Network was to prioritize what problems should be addressed. Clearly, determining whether V_T influenced patient outcomes was critically important, because the "statistical noise" generated by uncontrolled mechanical ventilation strategies could impair the assessment of all future testing of potentially beneficial therapies.

Another important decision made early on was that no authors would be listed for the major publications. Personal authorship would be reserved for studies involving secondary analysis of data from clinical trials. This decision precluded potential distractions and set a positive tone emphasizing organizational cohesiveness over competitiveness. It also kept the focus of the ARDS Network on the science and patient care. I always appreciated the fact that the ARDS Network made a concerted effort to ensure that the views of clinical coordinators were given a formal venue for expression. Coordinator's "front-line" insights were always accorded respect and consideration. Respiratory therapists (RTs) within the ARDS Network have been routinely consulted and have had substantial input into study/protocol design. Also, as with junior faculty, clinical coordinators always were encouraged to develop sub-studies that could be published as authored papers, to assist in their own professional development.

What Is the Legacy of the ARDS Network?

Since its inception the ARDS Network has published 7 major clinical trials that prospectively tested aspects of mechanical ventilation[1,22] practice, as well as fluid management[23,24] and various pharmacologic agents.[25-27] In addition, secondary analysis with data and specimens from these primary publications have resulted in numerous other publications that have helped expand our understanding of the pathophysiology and clinical management of ALI/ARDS. It is quite remarkable that, in a little over a decade, the studies undertaken by the ARDS Network have helped to answer many important questions regarding the management of ALI/ARDS (Table 2 and Fig. 1).

A New Approach to Clinical Trials in Critical Care

The ARDS Network has had a substantial impact on critical-care research. For the first time, the federal government created a network of university centers to carry out prospective Phase-III clinical trials of important, often non-pharmacologic, treatments in critical care (Table 3). As it did not involve potentially profitable drugs, a federally funded network was essential. The ARDS Network was designed in the same fashion as other federally funded, multicenter clinical networks that study cancer and cardiovascular disease. This is important as there is no federal institution specifically charged with directing critical-care research. Perhaps the success of the ARDS Network may one day lead to such a federally funded institution dedicated to the advancement of critical care.

Of particular importance, the ARDS Network represented a dramatic shift away from the conventional approach to clinical research of ARDS. Previous trials relied upon single institutions that were unable to provide definitive answers to important questions of clinical management, because they were under-powered and often poorly controlled in their methods.

One of the less-appreciated contributions of the ARDS Network was the use of a factorial design in critical-care research. The decision to study multiple interventions in a factorial design allowed concurrent Phase-II testing of promising new pharmacologic agents within larger Phase-III projects. In this way the ARDS Network was able to quickly test the potential benefits of drugs such as ketaconazole, lisophylline, and albuterol. If a promising therapy showed benefit in a Phase-II trial, it could be advanced seamlessly into a Phase-III study, whereas a negative trial would allow the ARDS Network to move quickly onto testing another agent. In passing, it should be noted that the initial ARDS Network studies were the first large-scale clinical trials to use the American-European Consensus Conference criteria to define ALI and ARDS.[4]

Creating a Strong Foundation for Clinical Research

An advantage of a federally funded clinical trials network is that it provides substantial financial support to hire sufficient numbers of clinical coordinators and administrative and biostatistical support. There was also modest financial support to assist junior faculty trying to establish their careers in clinical research. A crucial but less-appreciated aspect of this support is that it allowed ARDS Network investigators to meet regularly to discuss important issues of design, implementation, and interpretation of our clinical trials. I believe this was an important aspect of the ARDS Network's productivity, as it helped to build relationships among the investigators and fostered creativity and cohesion.

A crucial element of the ARDS Network organization was the purposive decision to bring in and mentor young investigators. This addressed an important need recognized by a previous National Institutes of Health conference.[20] So one of the most important legacies of the ARDS Network may not emerge for another decade. I believe that many of the future advances in our understanding and management of ALI/ARDS

Table 2. Contributions of 5 Major ARDS Network Studies to Understanding and Management of Acute Lung Injury

Study	Description and Major Findings
ARMA[1]	Compared low (6 mL/kg) to traditional (12 mL/kg) V_T ventilation. Provided convincing evidence that using a physiologic V_T titrated to a specific range of P_{plat} (25–30 cm H_2O): ↓ mortality ↓ pro-inflammatory mediators in the plasma ↓ days of non-pulmonary organ failure ↑ ventilator-free days ↓ ICU stay
ALVEOLI[22]	Compared a lower PEEP to a higher PEEP strategy, using a physiologic V_T titrated to the same range of P_{plat} (25–30 cm H_2O). The higher PEEP strategy: ↑ pulmonary oxygen-transfer function ↑ respiratory-system compliance No difference in pro-inflammatory mediator expression No difference in mortality No difference in ventilator-free days No difference in ICU stay The findings clearly suggest equipoise and strongly suggest that the *typical* patient with ALI/ARDS does not require more than moderate PEEP (approximately 10 cm H_2O) These findings were later confirmed by 2 large randomized controlled trials.[28,29]
LaSRS[25]	Tested high-dose corticosteroids versus placebo for the treatment of established ARDS (> 1 wk duration). Corticosteroids were found to: ↑ pulmonary oxygen-transfer function ↑ respiratory-system compliance ↑ ventilator-free days No difference in mortality No difference in infectious complications ↑ incidence of neuromuscular weakness These findings clearly suggest lack of efficacy of steroids in improving mortality. The benefits of improved lung function have to be balanced against the risk of prolonged neuromuscular complications.
FACTT[23]	Randomized management of fluid therapy, either via central venous catheter or pulmonary arterial catheter. Neither catheter was associated with either better outcomes or more complications. Equipoise established between central venous catheter and pulmonary arterial catheter to manage fluids in patients with acute lung injury.
FACTT[24]	Compared a fluid-conservative to a fluid-liberal strategy. The fluid-conservative strategy was associated with: ↑ pulmonary oxygen-transfer function ↓ lung-injury score ↑ ventilator-free days ↓ ICU stay No difference in mortality No difference in incidence of renal failure

ARMA = Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network low-tidal-volume (V_T) trial
P_{plat} = end-inspiratory plateau pressure
ICU = intensive care unit
ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury trial
PEEP = positive end-expiratory pressure
ALI = acute lung injury
LaSRS = Late Steroid Rescue Study
FACTT = Fluid and Catheter Treatment Trial

will come when the next generation of critical-care researchers, currently apprenticing under the auspices of the ARDS Network, steps forward onto center stage.

Another important decision by the ARDS Network was the systematic collection of biologic specimens in order to facilitate the study of the pathogenesis of ARDS. The wealth of specimens and physiologic information gathered from patients enrolled in the ARDS Network trials will continue to yield enormous amounts of information that can only help to expand our understand of ALI/ARDS. It is quite possible that some future breakthrough in the treatment of ALI/ARDS may be attributed in part to our refined understanding of pathogenesis culled from this vast store of biological samples.

The Impact on the Respiratory Care Profession

Several of us, who as RTs worked as clinical coordinators for the original ARDS Network, have noticed a pro-

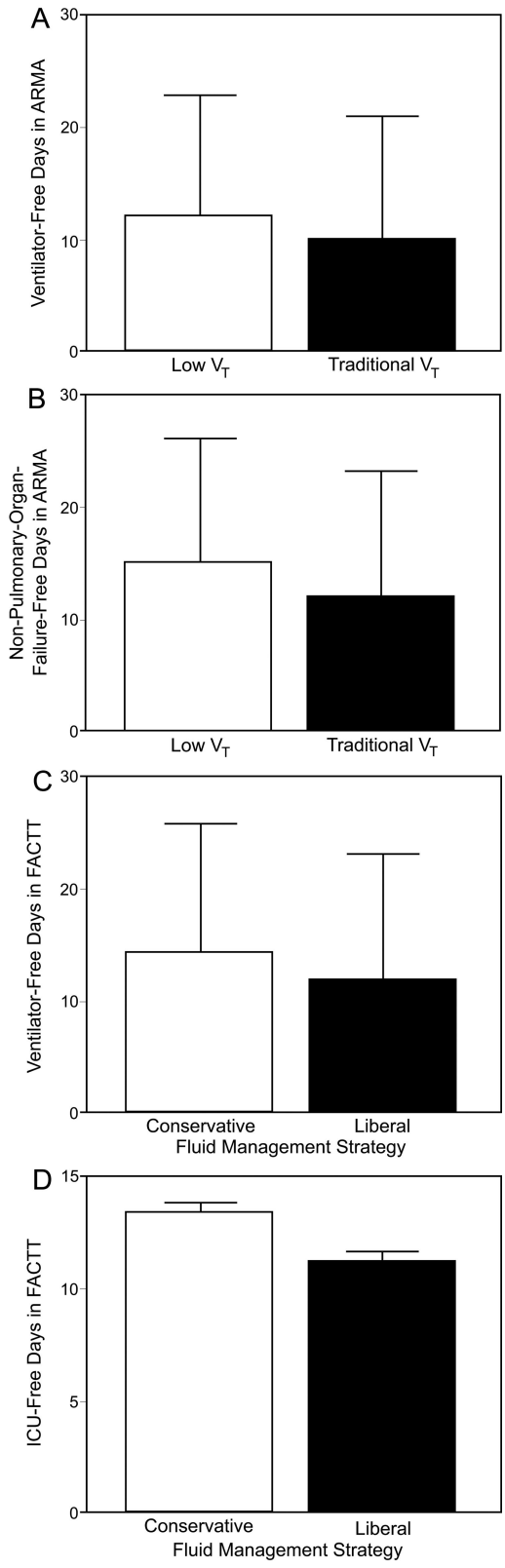

Fig. 1. Significant (non-mortality) outcomes from 2 clinical trials by the National Institutes of Health Acute Respiratory Distress Syndrome Network. During the trial of low tidal volume (V_T) (the ARMA study),[1] there was an increase in both ventilator-free days and non-pulmonary-organ-failure-free days associated with a low-V_T, lung-protective ventilation strategy (panels A and B, respectively). A conservative fluid-management strategy in the Fluid and Catheter Treatment Trial (FACTT)[24] increased ventilator-free days as well as the number of ICU-free days (panels C and D, respectively). ICU = intensive care unit.

found change in the attitude of physicians toward RT-driven protocols. Prior to the ARDS Network, we experienced stiff resistance to implementing any protocols governing mechanical ventilation. We've noticed that after the experience of the ARMA[1] and the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI)[22] trials at our institutions, the development and implementation of RT-driven protocols is now widely accepted. Of course, the weaning studies by Ely et al[30] and the Spanish Lung Failure Collaborative Group[31] also were instrumental in changing physician attitudes.

The ARMA[1] and ALVEOLI[22] studies clearly demonstrated that RTs are very capable of safely and effectively executing complicated protocols in critically ill patients. This compliment applies equally to our nursing colleagues, who executed a very complicated fluid-management protocol during the Fluids and Catheters Treatment Trial (FACTT) studies.[23,24] I believe that several decades from now the dedication and professionalism of both RTs and nurses during the ARDS Network studies will be seen as a turning point in our professional practices. It is clear that the future of medical practice is moving inexorably toward protocol-driven, evidenced-based care, and the experiences and mastery of protocols obtained during the ARDS Network trials will be seen as fundamental to that shift in practice. Your vigor in and fidelity to executing these protocols was absolutely pivotal to the success of the ARMA[1] and ALVEOLI[22] trials. Each of you who participated and facilitated that process share in this success, and I sincerely hope you are proud of your contribution to this historic accomplishment.

In addition, I believe that the ARDS Network was one of the first, if not the first, major clinical trials group that *routinely* employed RTs as clinical coordinators. Although at one time the role of clinical research coordinators was the sole purview of our nursing colleagues, RTs now are becoming more directly involved in the day-to-day management of large clinical trials. I hope this is a trend that will continue into the future, as it can only advance our profession further.

The Controversy

In late July of 2002 the NHLBI voluntarily suspended enrollment into the ARDS Network FACTT study,[23,24] at the request of the OHRP. This was based upon complaints

Table 3. Institutions Participating in the ARDS Clinical Trials Network

State	Institution
California	Moffitt-Long Hospital*†
	San Francisco General Hospital*
	University Hospital Fresno†‡
	University of California, Davis†
Colorado	University of Colorado Health Sciences Center*†
	Denver Health Medical Center*†
	Denver Veterans Medical Center*†
	Rose Medical Center*†
	St Anthony's Hospital†‡
Georgia	Emory University Medical Center†
Illinois	University of Chicago Medical Center‡
	Northwestern University Medical Center‡
Louisiana	Louisiana State University Health Sciences Center†‡
	Earl K Long Medical Center†‡
	Charity Hospital‡
	Alton-Ochsner Clinic Foundation†‡
	Our Lady of the Lake Hospital†
	Baton Rouge General Hospitals (Bluebonnet, Midcity)†
	Tulane University Medical Center†‡
Maryland	John Hopkins University Medical Center*
	University of Maryland Medical Center*
	Bayview Medical Center†
	Washington Hospital Center†
Massachusetts	Massachusetts General Hospital*
	Baystate Medical Center†‡
Michigan	University of Michigan Medical Center*
Minnesota	Mayo Clinics†
	Rochester Methodist Hospital†
	St Mary's Hospital†
North Carolina	Duke University Medical Center*†
	University of North Carolina Medical Center†‡
	Wake Forrest University Medical Center†‡
	Durham Regional Hospital†
	Moses Cone Memorial Hospital†‡
	Wesley Long Medical Center†‡
Ohio	Cleveland Clinic Foundation*†
	Metro Health Medical Center of Cleveland*†
	University Hospitals of Cleveland†‡
Pennsylvania	University of Pennsylvania Medical Center*
	Jefferson Medical College*
	University of Pittsburgh Medical Center‡
Tennessee	Vanderbilt University Medical Center*†
Texas	University of Texas Health Sciences Center‡
	Baylor College of Medicine†‡
Utah	LDS Hospital*†
	McKay-Dee Hospital*†
	Utah Valley Regional Medical Center†‡
Virginia	University of Virginia Health Sciences Center†‡
Washington	Harborview Medical Center*†
	University of Washington Medical Center†
British Columbia, Canada	Vancouver General Hospital‡
	St Paul's Hospital‡

* Original ARDS Network site (1996–2004)
† Current ARDS Network sites (2005 to present)
‡ Expanded ARDS Network site for Fluid and Catheter Treatment Trial (FACTT)
ARDS = acute respiratory distress syndrome

filed by 2 physicians at the National Institutes of Health over study design and the safety of subjects. A separate complaint letter reiterating the same concerns was filed a few days later by a citizen-based patient-advocacy group known as the Alliance for Human Research Protection. A superb chronicle of these issues can be found elsewhere.[32-34] I would like to take this opportunity to address some of the important issues related to this controversy.

Historical Revisionism and *Ex Post Facto* Medical Ethics

A disturbing aspect of the controversy was the use of control-group end-inspiratory plateau pressure (P_{plat}) data from the ARMA study[1] to accuse the ARDS Network of deviating from accepted norms of clinical practice *as they existed* in the mid-1990s.[5] In part, this criticism was based on the editorial[35] that accompanied the ARMA study,[1] which speculated that the mortality difference found in both the ARMA[1] and the "open-lung" ventilation trial,[36] but not in the other prospective trials[37-39] was due to a higher *mean* P_{plat}. In the control groups of the beneficial studies[1,36] the mean P_{plat} were 33 cm H_2O and 37 cm H_2O, respectively, compared to the P_{plat} of control groups in the non-beneficial trials[37-39] (27, 31, and 32 cm H_2O, respectively). This suggested that a $P_{plat} > 32$ cm H_2O was responsible for increasing mortality risk in ALI/ARDS. Setting aside the validity of using mean data to structure an ethical argument, a more basic question is whether data from a study designed 8 years beforehand should be used to criticize its ethics retrospectively?

It is crucial to recall that when the ARDS Network designed the ARMA study[1] (1994–1995) there was no consensus regarding airway pressure targets in the management of ARDS. For example, the 1993 Northbrook consensus conference on mechanical ventilation[40] stated only that "controversy exists regarding specific target levels [of P_{plat}, however] many would agree that a peak alveolar pressure greater than 35 cm H_2O raises concern regarding the development of barotrauma and ventilator-induced lung injury." This recommendation was based upon the assumption that, even in the presence of heterogeneous lung injury, it was probably safe to ventilate the lungs at or below total lung capacity, and this would correspond to a peak alveolar pressure of 30–35 cm H_2O.[41] However, this statement was made with the disclaimer that in clinical practice "the definition of a safe end-inspiratory volume is arbitrary."[41] Yet, other prominent opinion leaders in critical care suggested that peak alveolar pressure should be limited from 35–40 cm H_2O,[42] or 40–45 cm H_2O.[43] In fact, a major study[44] published in the late 1990s examined the role of V_T and airway pressures on the incidence of barotrauma in ARDS, and concluded that their findings in fact did *not* support the concept that "ventilatory pressures

should be limited to predefined values such as a static pressure of 35–40 cm H_2O, since conventional ventilatory pressures and volumes do not appear to affect the lungs adversely."

Following the publication of this[44] and 2 other prominent clinical trials from the mid-1990s,[36,38] the best clinical evidence still supported a recommendation that V_T reduction should occur in patients with severe ARDS when the P_{plat} was persistently greater than 40–50 cm H_2O.[45] As late as 1998, the second American-European Consensus Conference on ARDS[46] stated that "detailed clinical information is not available for guidance regarding the maximally safe peak and mean alveolar pressure," and despite the fact that ventilator-induced lung in jury could be demonstrated in an animal model, "this phenomenon has not yet been clearly demonstrated in humans."

Part of the controversy regarding an appropriate P_{plat} target is that ventilator-induced lung injury is caused by excessive lung tissue stress. Therefore, the relevant marker is transpulmonary pressure (alveolar pressure – pleural pressure). P_{plat} is an expedient but crude measure of respiratory system tension (lung-thorax) at end-inspiration, as it will not accurately reflect the magnitude of lung tissue stress when chest-wall compliance is diminished. Although it has been assumed that lung damage is the major source of decreased respiratory-system compliance in ARDS,[40] a recent review found most studies that examined respiratory-system mechanics in ALI and ARDS reported that chest-wall compliance was reduced by 50–80% from normal.[47]

What Constitutes a Best Practice Standard?

A closely related criticism of the ARMA study[1] was that our "traditional" V_T group, ventilated at 12 mL/kg predicted body weight (PBW) did not represent contemporary "routine" care in the mid-1990s. Instead, Eichacker et al[5] claimed that "current best practice standards" were 8–9 mL/kg PBW. Although setting V_T by body weight has guided practice from the inception of prolonged mechanical ventilation,[48] in daily practice this is done typically by subjective assessment rather than an actual measurement. Moreover, if V_T is set in mL *without* measuring a patient's actual or predicted body weight, then it is false to claim that clinicians possessed the *intention* of ventilating by a *specific target* in mL/kg. Prior to publication of the ARMA study,[1] setting V_T based upon predicted body weight was not part of routine clinical practice.

Eichacker et al[5] make an additional dubious claim that in the mid-1990s clinicians *systematically* altered V_T with the *intention* of controlling P_{plat} to a "routine care" range of 29–31 cm H_2O. Prior to the ARDS Network, the measurement of P_{plat} was not a uniform practice in respiratory care. For example, in the ARMA study more than 30% of patients had no clinical measurement of P_{plat} prior to study enrollment![49] And in a major, multicenter study of ARDS done in 1992–1993, P_{plat} was not even recorded.[44] Furthermore, there is no evidence that clinicians who routinely measured P_{plat} actually used that variable to control V_T.

What Constitutes an Appropriate Control Group?

What Eichacker et al[5] considered to be an appropriate control group for a lung-protective ventilation study requires further scrutiny. Their argument relied primarily upon pre-enrollment data from the ARMA study,[1] as well as a skewed interpretation[50,51] of previous survey data.[52] There are 2 fundamental problems with their approach. The first relates to a paucity of data, and the second relates to a well-known limitation stated by Carmichael et al[52]: "Surveys … do not document current practice, but rather only the respondents' beliefs about their practices. Self-reported behavior studies are limited by this factor and require follow-up with observational clinical studies to document activities."

Investigating the efficacy of any therapy in the critical-care environment requires that patients be enrolled rapidly before their disease advances. In the context of ALI/ARDS, the need for mechanical ventilation usually is the precipitating reason for admission to the intensive care unit. Typically, only 12–48 hours transpire from the onset of lung injury to study enrollment, so the amount of data available to gauge usual care practice is limited. The unproven assumption made by Eichacker et al[5] is that clinician-chosen ventilator settings (usually on the first day of ALI/ARDS) accurately portend subsequent clinician behavior over the course of a dynamic illness.

To investigate the validity of their assumption, I analyzed previously unpublished data from a study done at San Francisco General Hospital.[53] Although this is limited data from one center, I believe it is a valid reflection of what were the "current best practice standards"[5] during the ARMA study[1] at a participating center. If any institution should have been aware of the potential dangers from high-V_T mechanical ventilation, it was San Francisco General Hospital. Previously, we had published 2 landmark studies on mechanical ventilation and ARDS,[10,11] and our affiliate hospital at the University of California, San Francisco had published the seminal paper on ventilator-induced lung injury in an animal model.[6] San Francisco General Hospital instituted lung-protective ventilation in 1994, albeit inconsistently and only by allowing permissive hypercapnia in order to limit P_{plat} to $\leq$ 50 cm H_2O.

From 1998 through 1999, daily reference data of clinician-determined ventilator settings had been collected in 68 consecutive patients with ARDS who were not enrolled into the ARMA study and who survived at least 3 days

Table 4. Clinician Management of ARDS at San Francisco General Hospital 1998–1999

	Day 1	Day 3	*P*
V_T set (mL)	735 ± 123	758 ± 173	.20
V_T delivered (mL)	652 ± 119	677 ± 175	.18
V_T (mL/kg PBW)*	9.8 ± 1.7	10.2 ± 2.1	.23
P_{plat} (cm H_2O)	35 ± 8	36 ± 9	.45
PEEP (cm H_2O)	8 ± 3	9 ± 4	.4

* The calculation of delivered tidal volume (V_T) was done by investigators; this information was not part of routine clinical management and was not shared with clinicians.
ARDS = acute respiratory distress syndrome
V_T = tidal volume
PBW = predicted body weight
P_{plat} = end-inspiratory plateau pressure
PEEP = positive end-expiratory pressure

(Table 4). Of particular interest is the fact that P_{plat} on both the first and third days of ARDS was far higher than what Eichacker et al[5] claimed was being practiced during routine clinical care. Moreover, on Day 1 of ARDS, 44% of patients had a $P_{plat} > 35$ cm H_2O (average 42 cm H_2O, range 36–54 cm H_2O), whereas by Day 3, that portion had increased to 59% of patients (same average and range as on Day 1).

In addition, the limitations of using early clinical management data to construct a model for a control group based upon "routine care" became evident when the San Francisco General Hospital data were segregated by V_T ranges that approximated the criteria proposed by Eichacker et al[5]: a low-V_T strategy (< 8 mL/kg PBW), a routine-V_T strategy (8–9.5 mL/kg), and a traditional-V_T strategy (≥ 9.8 mL/kg). On Day 1 of ARDS only 37% of patients were managed with a "routine-V_T strategy," whereas 54% were ventilated with a traditional V_T strategy, while only 9% patients were ventilated with a low-V_T strategy (Fig. 2). Across all groups there was a wide variation in the resulting P_{plat} (Fig. 3).

Furthermore, between the first and third day of ARDS, the V_T of patients initially managed by "routine care" became highly variable (see Fig. 2). When data by initial V_T category were analyzed further, 56% of "routine care" patients had crossed-over to a traditional V_T strategy (Fig. 4) with a corresponding increase in P_{plat} (Fig. 5). In this subgroup of "crossover" patients the mean ± SD V_T increased from 8.9 ± 0.4 mL/kg PBW to 11.6 ± 1.9 mL/kg PBW ($P < .001$ via paired *t* test), whereas mean P_{plat} increased from 35 ± 8 cm H_2O to 38 ± 7 cm H_2O ($P = .26$). By contrast, only 25% of patients originally managed with a "traditional" strategy had their V_T reduced to the "routine care" range by Day 3 (from 10.6 ± 0.5 mL/kg PBW to 8.2 ± 1.6 mL/kg PBW, $P < .001$) with a nonsignificant decrease in P_{plat} (from 34 ± 9 cm H_2O to 32 ± 9 cm H_2O, $P = .63$).

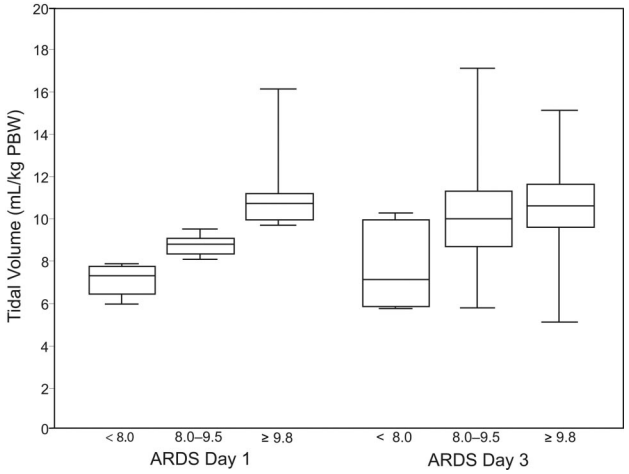

Fig. 2. Changes in clinician-selected tidal volume (calculated on the patient's predicted body weight [PBW]) from the first to the third day of acute respiratory distress syndrome (ARDS), based upon tidal-volume strategies defined by critics of the ARDS Network.[5] Each box represents the 25th-75th quartile, the line within the box represents the median, and the whiskers represent the range.

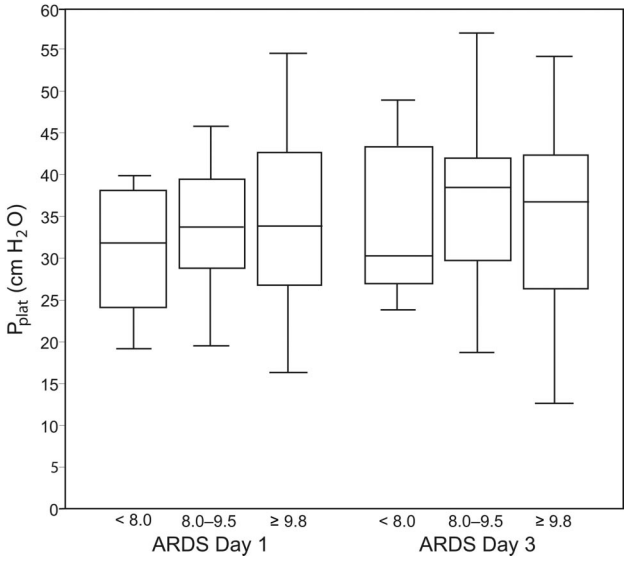

Fig. 3. Changes in plateau pressure (P_{plat}) from the first to the third day of acute respiratory distress syndrome (ARDS), based upon tidal-volume strategies defined by critics of the ARDS Network.[5] The category assignment is based on the day-1 tidal-volume data.

These results suggest 2 things. First, during the last 2 years of the ARMA study,[1] at a participating site, clinicians routinely managed a substantial number of patients with ARDS with both a V_T and P_{plat} far in excess of what Eichacker et al[5] claimed were "current best practice standards" ostensibly being followed at ARDS Network sites. Second, that a substantial number of patients whose initial V_T changed from a "routine" to a "traditional"-sized breath (and vice versa) by the third day of ARDS suggests that

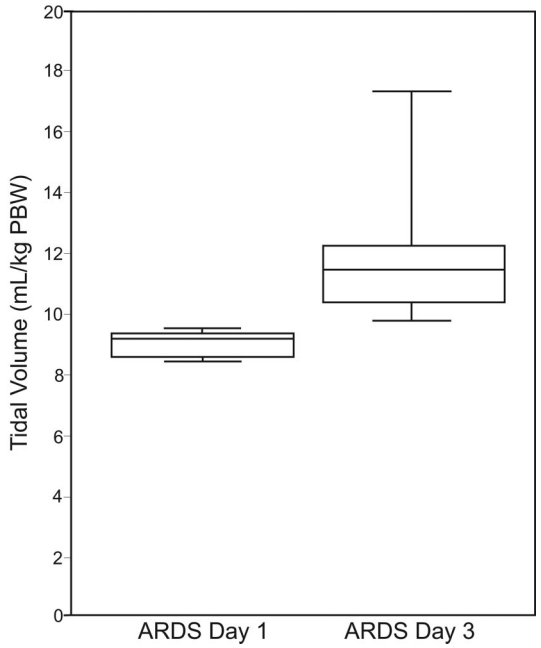

Fig. 4. Changes in tidal volume (calculated on the patient's predicted body weight [PBW]) among a subgroup of patients with acute respiratory distress syndrome (ARDS) receiving "current best practice standards" (tidal volume of 8–9 mL/kg) but who were crossed over by clinicians to a traditional tidal volume approach.

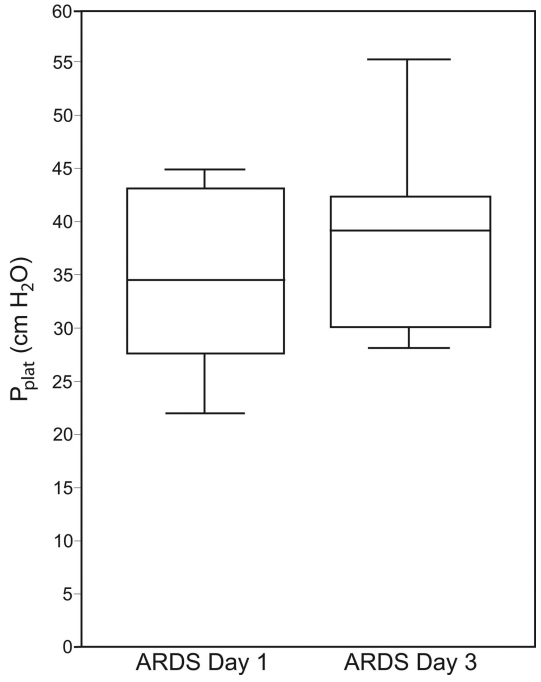

Fig. 5. Changes in plateau pressure (P_{plat}) among patients with acute respiratory distress syndrome (ARDS) receiving "current best practice standards" (tidal volume of 8–9 mL/kg predicted body weight) but who were crossed-over by clinicians to a traditional tidal volume approach.

assumptions regarding normative mechanical ventilation strategies should not be based upon "snap-shot" data from early in the disease course.

These data have serious implications for those attempting to define "best practice standards" in order to construct a "control group" for prospective clinical trials. The substantial variance in V_T strategy used by clinicians supports the arguments made by those advocating the need for protocolized care during the American-European Consensus Conference of 1994.[4] Wide variation in clinician practice, not only between patients, but also temporally within individual patients, renders the results of any non-protocolized "usual care" group uninterpretable. Attempting to design control groups based upon "best practice standards" is a worthy goal, but it will be useful only if such practices can be accurately and realistically described.

Human Subjects Protection During Clinical Research

The official investigation by the OHRP ended with the exoneration of the ARDS Network by 2 panels of experts regarding the issue of a preexisting "standard of care." Yet, another part of the controversy revolved around human subjects' protection. To be clear, this issue already was of national concern prior to the ARDS Network controversy.[54] In 1992 the NHLBI conference on ARDS[20] devoted considerable attention to the feasibility of consenting critically ill patients with diminished cognitive capacity into clinical trials. Conference participants "lamented" the variability in policies regarding consent. This was believed to be due to a lack of communication between institutions and local authorities responsible for overseeing this process. Conference participants called for the development of uniform national standards to guide local policies at institutions undertaking clinical trials for the study of ARDS.

At the center of the controversy over informed consent was ambiguity regarding who could *legally* provide consent for critically ill patients to be enrolled into a clinical trial. Since the early 1990s, consent of cognitively impaired subjects has followed "The Common Rule," which stipulates that impaired subjects cannot be enrolled without investigators first obtaining "legally effective informed consent" from the subject's "legally authorized representatives."[55] This was defined as an "individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject." Unfortunately, "applicable law" has never been defined in detail, leaving it open to interpretation. Historically, family members have acted as surrogates in the consent process. Nonetheless, they are not specified as legally authorized representatives (parents of minors being the exception) for research purposes under most state laws. In the past, the OHRP had permitted institutional review boards to allow surrogate consent for

research, based upon the fact that state laws permit surrogate consent for medical treatment.[34]

As a result of the ARDS Network controversy, California became one of the first states to pass specific legislation addressing the issue of informed consent for research purposes.[34] In addition, the controversy was the impetus for a major conference sponsored by the American Thoracic Society, aimed at improving human subjects protection during clinical trials, particularly as they relate to critical-care research.[55] Several members of the ARDS Network have been deeply involved in working to improve human subjects protection in medical research.[55-58]

Cultural and Political Dimensions of the Controversy

Despite the fact that the ARDS Network was exonerated by the OHRP, and that the methods of Eichacker et al[5] were criticized,[32,50,59-62] nevertheless they have found support among a segment of the critical care community.[63-65] There are several potential explanations for this support. I'll restrict myself to speculating upon only two of these possibilities. First, in regards to our own profession, RTs have a passionate interest in mechanical ventilation. Within our subculture there is a powerful, largely unacknowledged belief that mechanical ventilation in ARDS is not merely supportive therapy, but is curative. In some respects our inquisitiveness and enthusiasm regarding new modes of ventilation and other techniques take on the attributes of a quasi-religious quest. Yet, that belief is not shared by the majority of the critical care community, including ARDS Network investigators. I believe our advocacy[66] for widespread adoption of the ARDS Network protocol into clinical practice was viewed as a threat. RTs as well as physicians with a profound interest in mechanical ventilation may have interpreted this as a call to cease all other endeavors in lung-protective ventilation. Thus, when the controversy broke, there were clinicians quite prepared to accept the criticisms of Eichacker et al,[5] with little reflection as to their merits.

Second, I believe that the credibility given to the criticisms raised by Eichacker et al[5] may be motivated by a larger controversy over the role of evidence-based medicine in clinical practice. I believe many clinicians perceive evidence-based medicine as a threat to their professional autonomy, while others are concerned about the scientific merit governing the construction of a hierarchy of evidence.[67] Although medicine as an art form has been practiced for millennia, the beginnings of "therapeutic science" date back only to the 19th century.[68] At the beginning of the 21st century we are witnessing a dramatically intensified struggle between medical art and medical science. In my opinion, the controversy over the ARMA[1] and FACTT[23,24] studies represents the first major salvo in this battle. Viewed from this context, the criticisms by Eichacker et al[5] provided easy ammunition to opponents who enthusiastically used the controversy to try to undermine the credibility of evidence-based medicine.

Finally, from a philosophical standpoint, controversy legitimately can been viewed as a sign of intellectual "vitality" that ultimately serves to strengthen science.[69] Unfortunately, the manner in which the ARDS Network controversy unfolded suggests a less sanguine view. When poorly constructed arguments are given a prestigious venue, both scientific debate and clinical practice may suffer. This is particularly true when, regardless of intent, the controversy is used by others[70] for purely political ends, and is sensationalized by biased media coverage.[71] To be clear, the ARDS Network controversy had the potential to seriously threaten state-of-the-art clinical research.[72] The problem of politicizing science became distressingly apparent when my own research,[73] as well as the editorial of a colleague,[74] were misrepresented by a political advocacy group[75] in order to attack both the ARDS Network and lung-protective ventilation. In my opinion, these tactics diminish the possibility for honest scientific debate, transforming it instead into partisan intellectual warfare. Paradoxically, controversy can promote defensiveness and invite self-censorship, particularly to those who do not wish their work or opinions to be used unjustly as weapons against either colleagues or positions they in fact support.

Summary

There are several aspects to the legacy of the ARDS Network. First and foremost, the ARMA study[1] was the first major breakthrough in the treatment of ARDS, as it provided convincing evidence supporting the use of lung-protective ventilation. Moreover, the creation of a federally funded clinical trials network specifically devoted to Phase-III clinical trials in critical care was novel and allowed the testing of important, non-pharmacologic therapies that otherwise would never have been done. It also pioneered the use of factorial design in critical-care studies to allow efficient Phase-II testing of promising therapies. Other important aspects of the ARDS Network include mentoring a new generation of critical-care researchers, as well as collecting an enormous store of biological samples that inevitably will advance our understanding of pathogenesis. Some day this may lead to another therapeutic breakthrough in treatment for ARDS.

An unanticipated outcome has been the opening of a dialog on the design of clinical trials in critical care, as well as a concerted effort to improve the protection of subjects enrolled into those trials. Finally, in regards to the respiratory care profession, the successful implementation of complicated RT-driven protocols has only enhanced the

stature of RTs. Already this has begun to advance the use of other RT-driven protocols in clinical practice. I invite the interested reader to visit the ARDS Network web site to learn more about the clinical trails network (http://www.ardsnet.org/front).

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