

# Multicenter clinical research in adult critical care

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**Objective:** To describe the development, organization, and operation of several collaborative groups conducting investigator-initiated multicenter clinical research in adult critical care.

**Design:** To review the process by which investigator-initiated critical care clinical research groups were created using examples from Europe, Australia, the United States, and Canada. Various models of group structure and function are discussed, highlighting complementary approaches to protocol development, multicenter study management, and project funding.

**Data Sources:** Published peer review research and unpublished terms of reference documents on the structure and function of these groups.

**Data Synthesis:** The overall goal of clinical critical care research groups engaged in multicenter studies is to improve patient outcomes through conducting large, rigorous investigations. Research programs we reviewed included the following: a) multicenter epidemiologic studies and surveys; b) technology evaluations of mechanical ventilation; c) investigations focused on three priority fields (acute lung injury, infection, and acute brain injury); d) a series of randomized trials of treatments for one syndrome (acute respiratory distress syndrome); and e) diverse

methodologies addressing several clinical problems. The structure and function of these research groups differ according to their historical development, research culture, and enabling resources. Specific protocols emerge from clinical questions generated by investigators or from collectively prioritized research agendas. Project funding includes government support, peer-review grants, intensive care foundations, industry, local hospital funds, and hybrid models. Infrastructure for study management varies widely.

**Conclusions:** Several national and international groups have engaged in investigator-initiated multicenter critical care research. The development, organization, and operational methods of these groups illustrate several collaborative models for clinical investigations in the intensive care unit. Common characteristics of these groups are a cohesive spirit, a sense of mission to achieve shared research goals, and acknowledgment that such an organization is much more than the sum of its parts. (Crit Care Med 2002; 30:1636–1643)

**KEY WORDS:** critical care medicine; intensive care medicine; randomized clinical trial; observational studies; clinical research

The high morbidity and mortality associated with critical illness has stimulated a wealth of studies that form the foundation of daily practice. Clinical research in the intensive care unit (ICU) has helped us to better understand myriad disease processes, how we may detect and modify them, and how these processes relate to patient outcomes. Issues of epidemiology (1), diagnosis (2), prognosis (3), prevention (4), treatment (5), and process of care (6) central to the care of

critically ill patients have been addressed in numerous multicenter studies.

Multicenter collaboration can result in higher rates of patient enrollment than single-center research, thereby generating larger studies or studies of shorter duration. Larger studies are more likely to be published than studies with small sample sizes (7), potentially increasing awareness of research findings in the clinical and research community. Enrollment of patients in several sites also enhances the generalizability of study results to similar patients in similar settings.

The objective of this review article is to describe several aspects of multicenter clinical research in adult critical care medicine. Domains that will be addressed include the development of collaborative groups (the rationale for their formation and the process by which they are constituted), their organization (both structure and function), and their methods of operation (the creation, management, and funding of their research programs). Our

focus is several established clinical research groups in Europe, Australia, United States, and Canada that are engaged in investigator-initiated multicenter studies.

## METHODS

This article is structured according to a series of five questions commonly asked about the development, organization, and operation of critical care clinical research groups: a) *Why* were these research groups developed, and *which* clinical problems have they addressed?; b) *How* were these research groups constituted?; c) *How* are protocols developed by these research groups?; d) *Where* do these research groups obtain project funding?; and e) *What* study management methods are used by these research groups?

These groups were selected based on the following: a) their contributions to adult critical care research; b) conduct of investigator-initiated studies; and c) presentations at a symposium of the American Thoracic Society Meeting on Clinical Trials in Critical Care on May 10, 2000, in Toronto, Canada. Groups

From the Departments of Medicine & Clinical Epidemiology, McMaster University (DC), Hamilton, Ontario, Canada; Department of Medicine, Johns Hopkins University (RB), Baltimore, MD; Department of Intensive Care and Hyperbaric Medicine, Alfred Hospital, Monash University (JC), Melbourne, Australia; Service de Réanimation Médicale, Hôpital Henri Mondor, AP-HP, Université Paris-Val de Marne (LB), Créteil, France; Department of Intensive Care, Erasme University Hospital, Free University of Brussels (J-LV), Brussels, Belgium.

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represented include the following: a) international investigators conducting epidemiologic studies and surveys; b) European mechanical ventilation consortia; c) the Australia & New Zealand Intensive Care Society Clinical Trials Group (ANZICSCTG); d) the Acute Respiratory Distress Syndrome Network (ARDSnet); and e) the Canadian Critical Care Trials Group (CCCTG).

Data sources we considered for this report were texts of symposium presentations, peer review publications authored by these groups, including randomized clinical trials (RCTs), observational studies, and surveys. Organizational information on structure and function was obtained from internal terms of reference documents.

## RESULTS

*Why Were These Research Groups Developed, and Which Clinical Problems Have They Addressed?* The primary, overarching reason for developing these clinical research groups is to enhance understanding of how complex disease processes can be optimally and safely diagnosed, monitored, attenuated, or cured. The desire to conduct large, rigorous, generalizable clinical studies in the ICU is the fundamental motivation for these multicenter investigations, which are developed to improve the outcomes of critical illness. Unique and complementary health problems have been addressed by these research groups.

Several multicenter European ICU studies have provided key data on the prevalence of diseases and prevailing practice patterns. The theme of emerging pathogens in critically ill patients prompted the European Prevalence Study of Infections in the Intensive Care Unit, in which 45% of patients in 1,417 ICUs were considered to be infected, and more than 20% of patients were found to develop an ICU-acquired infection (8). Other multicenter observational studies have documented a growing incidence of antibiotic resistance among bacterial isolates in western European ICU patients (9). The Sequential Organ Failure Assessment Study was conducted to record the incidence of organ dysfunction in 1,449 patients followed prospectively for their entire ICU stay (10). Recently, the Anemia and Blood Transfusion in the Critically Ill study was conducted to describe blood transfusion practices on 3,534 patients in 146 Western Europe ICUs. The study revealed that 37% of patients received a transfusion during their ICU stay. The transfusion rate was 42%

among patients in the initial 28 days and 73% in patients who stayed  $\geq 1$  week in the ICU. Moreover, there were significant associations between blood transfusions, morbidity, and mortality.

In addition to cross-sectional and longitudinal observational studies on infection in critically ill patients, European surveys have described the application of key ethical principles in diverse cultures regarding care at the end of life (11, 12).

The theme of applied physiology is central to the longstanding European mechanical ventilation consortia. Understanding the administration and withdrawal of ventilation requires integrating knowledge about respiratory physiology, biomechanics, and the patient-technology interface. Observational studies by these consortia have identified variation in the modes of ventilation and weaning in Europe (13, 14) and a wide ranging incidence of the acute respiratory distress syndrome (ARDS) (15, 16). Randomized trials have limited tidal volume to prevent ventilator induced lung injury (17), tested noninvasive ventilation for patients with chronic obstructive pulmonary disease exacerbation (18), assessed the efficacy of continuous positive airway pressure to prevent endotracheal intubation in patients with acute lung injury (19), and evaluated different approaches to weaning from mechanical ventilation (20, 21). Advances in our understanding of weaning have been made by different research groups arriving at different conclusions about the effectiveness of various weaning techniques (22, 23). An important insight derived from these disparate results is that the modes of weaning may not influence outcome as much as the way that the modes are actually used.

The ANZICSCTG was formed in 1994. Strategic research initiatives of the ANZICSCTG focus on three priority areas: acute lung injury (ALI), infection, and acute brain injury. The general approach is to begin with demographic surveys in Australia and New Zealand to furnish relevant data for future RCTs. The first prospective utilization review of antimicrobials in the ICU demonstrated that 80% of surgical patients received antibiotic prophylaxis and that 38% of all patients receiving antibiotics had systematic inflammatory response syndrome or suspected infection; moreover, mortality was lower than that predicted by simplified acute physiology II scores (24). Two additional observational studies, which

measured the incidence of ALI and ARDS and the incidence of sepsis and the systematic inflammatory response syndrome, are completed but not yet submitted for publication. In the first double-blind RCT of the ANZICSCTG, 328 patients with early renal dysfunction and systematic inflammatory response syndrome were randomized to receive dopamine 2  $\mu\text{g/kg/min}$  or placebo; renal and mortality outcomes were the same in both groups (25). A second double-blind RCT compares albumin vs. normal saline for resuscitation of ICU patients. Following the Cochrane Injuries Group meta-analysis, which reported a 6% (95%CI, 3%–9%) absolute increase in mortality associated with albumin (26), this study will enroll 7,000 patients in 19 ICUs in Australia and New Zealand and is designed to detect a 3% mortality difference. A third ongoing Australian RCT tests hypertonic saline in addition to standard therapy for prehospital resuscitation of head-injured patients with traumatic coma and hypotension. This 3-yr study of ANZICSCTG investigators includes all hospitals in the city of Melbourne. Neurologic outcome 6 months after injury is the primary outcome (27).

ARDSnet was developed in 1994. The goal of ARDSnet is to conduct clinical trials of promising treatments for ARDS and related conditions. The first double-blind RCT evaluated the thromboxane synthetase inhibitor and 5-lipoxygenase inhibitor ketoconazole for treatment of patients with ALI and ARDS. There were no significant effects of ketoconazole on mortality, ventilator-free days, organ failure-free days, pulmonary physiology, or adverse events (28). The second RCT compared traditional tidal volume (12 mL/kg predicted body weight) vs. lower tidal volume (6 mL/kg predicted body weight) ventilation in 861 patients with ALI and ARDS (29). This RCT was stopped early because of a significant reduction in mortality using low tidal volume ventilation (40% vs. 31%,  $p = .007$ ) and more ventilator-free days in the first 28 days ( $p = .007$ ). A third RCT assessed effects of lisofylline vs. placebo in patients with ALI and ARDS. There were no significant effects of lisofylline on mortality or ventilator-free days (30).

The CCCTG was created in 1989 to improve the care of critically ill patients through investigator-initiated research. An additional reason for the formulation of this group was to provide a national forum for continuing education about re-

search methods (31). The portfolio of published CCCTG research programs include end-of-life care (32–34), blood transfusions (35–38), enteral nutrition (39), and a 10-yr program on stress ulcer bleeding and ventilator-associated pneumonia. The latter program illustrates the importance of observational research to prepare adequately for a subsequent RCT (40). Background observational studies created reproducible bleeding definitions (41), estimated bleeding incidence rates (42), measured the clinical and economic importance of target outcomes (43), ensured randomization of patients at high risk of bleeding rather than those unlikely to benefit from prophylaxis, and allowed for sample size estimates reflecting realistic expected differences between ranitidine and sucralfate (44). This research program also demonstrated how preplanned observational analyses on RCT databases can help to interpret RCTs (45), by validating the length of ICU stay and mortality attributable to bleeding (46), re-examining bleeding risk factors (47), estimating the length of ICU stay and mortality attributable to VAP (48), determining risk factors for VAP (49), and evaluating the influence of VAP diagnostic approaches on patient management (50).

*How Were These Research Groups Constituted?* Well-established European cooperation on the organization, delivery, and education of intensive care led naturally to collaborative research projects. Investigators of the international epidemiologic studies and surveys and the European mechanical ventilation consortia are considered together in this section. These researchers have the opportunity to meet frequently at the Brussels International Symposium on Intensive Care and Emergency Medicine, the European Society of Intensive Care Medicine Meeting, and other national conferences. Diverse models of collaboration have emerged.

A unique and successful model for cross-sectional prevalence studies has been an open invitation for any ICU in Europe to participate, such as that used for the European Prevalence Study of Infections in the Intensive Care Unit. Some European research groups are comprised of colleagues with longstanding shared interests and expertise and have generated projects such as the Sequential Organ Failure Assessment study, which was designed to describe the epidemiology of organ failure in critically ill patients. Re-

cently, Internet sites such as *intensive.org* helped to identify participants for the Anemia and Blood Transfusion in the Critically Ill study on red cell transfusions.

Although initially multicenter European research was conducted independent of specific societies, established networks were eventually used to obtain the support of national and European professional entities. For example, the Sequential Organ Failure Assessment study was endorsed by the European Society of Intensive Care Medicine. Early projects of the mechanical ventilation consortia were not commissioned by federal, regional, or professional agencies. Recently, however, the French Society (Societe de Reanimation de Langue Francaise) and the European Society (European Society of Intensive Care Medicine) supported collaborative surveys throughout Europe (13–15).

The ANZICSCTG was formed by the Australian & New Zealand Intensive Care Society (ANZICS) after many years of collaboration on administrative and educational aspects of intensive care. Members of the ANZICSCTG are multidisciplinary intensivists from Australia and New Zealand who also have a shared binational database. Executive members include both state and federal ANZICS representatives. The ANZICSCTG meets twice per year to develop and refine protocols. There is no federal or regional infrastructure funding for ANZICSCTG, but some support is afforded by the ANZICS Intensive Care Foundation (*vide infra*).

ARDSnet was created by the United States National Institutes of Health National Heart, Lung, and Blood Institute (NIH NHLBI). In 1993, NIH issued requests for proposals from potential clinical centers for ARDSnet. Applicants required a track record of enrolling 40 patients/yr in ICU studies, availability of 200 patients/yr with ARDS, the potential to enroll 40 patients/yr in ARDSnet trials, and a record of the investigator's scientific accomplishments. Ten ARDS Network centers were selected from 41 applications. A coordinating center was also selected in 1994. An additional ten clinical centers were added in 2000. The NIH created a formal organizational structure in which a steering committee comprised of voting representatives from each of the ten clinical centers, the coordinating center, and the NIH NHLBI Lung Division Staff is the central decision making body. Standing committees of the steering committee include the executive, protocol, natural history, pathogenesis,

ethics, institutional review, and publications committees. Two independent committees that report directly to the NIH are the protocol review committee and a data safety monitoring board.

For many years, the Canadian Medical Research Council has made seed grants available to sponsor exploratory meetings of new research groups. Thus, MRC Canada supported the inaugural open invitation meeting of the CCCTG at which a simple organizational structure was adopted, consisting of a chair and scientific and administrative executive committee. Candidate protocols were discussed, and a prognosis study on gastrointestinal bleeding was chosen for the first project. Administration of the CCCTG has since been supported through modest membership fees. All Canadian ICU practitioners representing numerous clinical disciplines including medicine, anesthesia, surgery, pediatrics, and nursing are welcome. The clinical experience of CCCTG physicians ranges from ICU fellows to senior intensivists. Research experience ranges from beginners to established investigators. Several members also have formal training in epidemiology, biostatistics, economics, and qualitative research. The function of the CCCTG executive is to provide scientific and administrative support to the membership throughout the year and aid in grant and manuscript preparation. Centers participating in CCCTG research differ for each study based on the center's clinical expertise, documentation of the requisite incidence of the problems of interest, research expertise, and commitment to protocol adherence and study completion.

*How Are Protocols Developed by These Research Groups?* Considering the international epidemiologic studies and surveys as well as the European mechanical ventilation investigations, protocols are usually developed by investigators who have collaborated previously. Studies are designed by these multicenter research groups using several models. For some studies, shared interests and expertise facilitate protocol development by a core group of established researchers and invited junior colleagues. Senior scientists often form advisory committees for these projects to help with protocol refinement. The European community is large and diverse enough to select several important research questions and advance several research programs concurrently (e.g., sepsis, end-of-life care,

modes of ventilation, and weaning methods).

Protocols of the ANZICSCTG group are usually first debated using a closed *listserv* and then presented formally to members at the biannual meetings. They reflect the three established priorities of the ANZICS Foundation (ALI, infection, and traumatic brain injury) and a recent fourth focus on prevention of complications of critical illness. Each of these areas are guided by working parties comprising established investigators who design each project. RCT design to date has not protocolized ancillary clinical management.

ARDSnet has a more complex protocol development process. At the first ARDSnet meeting, a protocol review committee prioritized the 20 RCTs proposed by the ten clinical centers in their competitive applications for ARDSnet membership. The steering committee considered the strength of the preclinical and early clinical data supporting the new therapies, experience at one or more of the centers with the new therapies, and potential to inform clinical practice for a large numbers of patients. Interest was greatest for lung protective ventilation strategies for ALI and ARDS; two centers were already conducting small RCTs of small tidal volume strategies that provided invaluable experience for a large, more definitive study (51). Although multicenter mechanical ventilation trials were considered to be extremely challenging, a successful trial would provide information for controlling key aspects of care in all concurrent or subsequent RCTs of nonventilatory treatments. For these reasons, ARDSnet proceeded with the RCT of traditional vs. lower tidal volume ventilation. An RCT of ketoconazole vs. placebo was adopted based on results of two smaller RCTs in which ketoconazole appeared to prevent ARDS in patients at risk of ALI (52, 53); in addition, one of the ARDSnet centers had contributed to the preclinical evaluation of ketoconazole as a potential anti-inflammatory agent (54).

CCCTG protocols are developed throughout the year by any CCCTG member. Protocols in various stages of development for new studies are precirculated to members and the executive in advance of the biannual meetings and are presented in detail to the entire membership. Active discussion at the meeting ensues to provide constructive criticism representing diverse, collective CCCTG

membership views on issues of relevance, methodology, statistics, implementation, and ethics. Protocols are thus iteratively and cooperatively developed and refined. At each meeting, each protocol is voted on to determine CCCTG affiliation. Protocols pursued under the auspices of the CCCTG undergo additional internal review by the CCCTG executive before peer-review grant submission.

*Where Do These Research Groups Obtain Project Funding?* The European Prevalence Study of Infections in the Intensive Care Unit was conducted on a voluntary basis with no financial remuneration to the investigators, but data analysis and presentation was sponsored by a pharmaceutical company. The Sequential Organ Failure Assessment study was also executed largely on a volunteer basis, with a limited grant from the European Society of Intensive Care Medicine. The Anemia and Blood Transfusion in the Critically Ill study was also sponsored by a grant from the pharmaceutical industry. Although the European community has peer-review funds to support international studies, they tend to be allocated toward health problems such as cardiovascular disease and cancer; thus, these resources are not readily available for international intensive care studies in Europe. Costs for these types of studies are often minimized through involvement of research fellows in data collection.

Initial projects of the mechanical ventilation consortia were not funded by federal, regional, or professional agencies, although some studies have received grants-in-aid from ventilator companies or the pharmaceutical industry. Modest resources have been obtained from the French Society (Société de Réanimation de Langue Française) and the European Society of Intensive Care Medicine for nonexperimental studies. In France, a government agency called the Clinical Research Hospital Project was created in 1993 to specifically fund such investigations; this agency may support future investigations in this field. However, relative to costs for similar multicenter studies elsewhere, mechanical ventilation studies have received only modest external resources. The drive to complete studies is fueled by academic motivation across centers and commitment to collaborative research.

The first ANZICSCTG studies were conducted with minimal funding and depended on a small number of research

nurses established to run earlier industry-sponsored trials. The ANZICS Foundation previously provided grants for young investigators for many years using funds generated from the Annual Scientific Meeting. However, in 1998, ANZICS upgraded the Foundation to be an ongoing major source of funds for intensive care research and the clinical trials group. The first phase of a novel, highly successful fundraising campaign involved obtaining donations from trade companies and establishing a Foundation Manager. Subsequently, banks, the Australian Business Council, department stores, a television company, and print media were recruited. Recently, a patron of ANZICSCTG was announced: the Australian of the Year, Professor Sir Gustaf Nossal. The marketing strategy highlighted that approximately 100,000 ICU patients are treated annually in Australia and New Zealand, and the 85% survival results in 60,000 citizens that are alive each year because of intensive care. The aim of research sponsored by ANZICSCTG is thus to increase overall survival by 2% to save an additional 2,000 lives annually. A 10 million dollar target over 3 yrs is the current goal, which is likely to be achieved. Meanwhile, the large albumin vs. saline RCT is funded by the National Health and Medical Research Council, and the hypertonic saline RCT is funded by the National Health and Medical Research Council, the ANZICS Foundation, and other regional grants.

The major source of funding for ARDSnet is the U.S. NIH NHLBI. Funds support substantial efforts by program coordinators and investigators involved in protocol preparations and submission for institutional review board approval, recruitment, protocol implementation, pharmacy support, and manuscript preparation. Substantial funds are also provided to the ARDSnet coordinating center for biostatisticians, data managers, a program manager, and a clinical director. Funding for the ARDSnet exceeds the support available to the other critical care trials groups described herein. This allowed ARDSnet to undertake large studies in ARDS to detect modest yet realistic treatment effects. With substantial support for recruitment and data collection, each of the ten clinical centers was able to recruit about 30 patients/yr for the traditional vs. low tidal volume RCT. ARDSnet was also able to implement sophisticated data management and quality control systems that could not be accom-

plished otherwise, which helped to ensure the integrity of the data.

CCCTG projects have been funded by peer-review agencies (national, provincial, and regional), technology and pharmaceutical industry, hospitals, and over-heads from ICU clinical billings. Fundraising efforts directed at private and public sectors have created the Canadian Intensive Care Foundation, which sponsors an annual peer-review grant competition for clinician-investigators in their first 5 yrs of practice. Many of these projects are pilot studies for future large-scale investigations. However, the most common funding strategy for studies of the CCCTG is hybrid sources. After serious cuts by Canadian granting agencies to clinical investigations (55), renewed investment in this genre of research has begun.

*What Study Management Methods Are Used by These Research Groups?* Typically, the large epidemiologic studies and surveys conducted in Europe are managed by a small number of experienced professionals at a few centers. Instead of clinical research organizations or agencies, local investigators or research fellows take responsibility for the integrity of data collection. Analyses are usually supervised by university, hospital, or industry-based statisticians. For each of these groups, electronic and other communication vehicles are used to aid study management.

The European mechanical ventilation consortia studies are generally conducted without official clinical research organizations and without formal centralized infrastructure services, often with the organizational help of French and European Intensive Care Societies. In any case, an efficient and experienced set of research staff at a few central coordinating hospitals organized the published studies; these centers were responsible for data validity checks, data entry, and analysis. Investigators generally met during the annual meetings of the scientific societies.

Before 1999, the ANZICSCTG used conventional study management methodology and coordinated each trial from one of the study hospitals. The more ambitious recent RCT of albumin vs. normal saline in the ICU has enabled a research partnership with the Institute for International Health in Sydney. The Institute provides experience with management of very large RCTs and access to newer computerized data management systems.

The coordinating center of each ARDSnet study provides trial design and biostatistical advice, case report forms, randomization systems, data analyses, protocol quality control documents, and reports for Data Safety and Monitoring Board analyses. ARDSnet has implemented computerized case report forms for direct computer data entry. Data are transmitted electronically each week to the coordinating center. The quality of protocol adherence in ongoing studies is monitored by comparing randomly selected parameters to values required by protocol. This allows the coordinating center to provide real-time feedback to the clinical centers regarding protocol conduct that requires attention and improvement. This approach is one of the most sophisticated data management strategies ever utilized in multicenter clinical research in critical care.

Each subgroup of investigators in the CCCTG has its own methods center and study management strategies. This decentralized approach maximizes the study management experience for each set of investigators, facilitates management strategies tailored to each project, and is crucial for developing autonomous administrative leadership skills, particularly among junior investigators who frequently lead CCCTG projects. Vehicles for data collection include computerized and paper case report forms, datafax, handheld devices, and Web-based methods. The CCCTG has used a multiproject, uni-center perspective to evaluate accrual into studies operating in each site. A Screen Log was tested as a tool for monitoring eligibility and enrollment of patients in four multicenter randomized trials on stress ulcer prophylaxis, blood transfusion, immunotherapy for sepsis, and mechanical ventilation (56). A taxonomy of reasons for nonenrollment into each RCT was created, enrollment efficiency rates were calculated, the influence of each RCT on enrollment into the other RCTs was measured, and study-specific strategies to maximize accrual in each RCT were established. Variations on the theme of this Screen Log have fostered communication and continuous quality improvement initiatives for the management of ICU studies concurrently conducted across Canada.

The final stage of study management after analysis and interpretation of the data involves the dissemination of study results. Conventional dissemination vehicles include peer-review presentations,

abstracts, and peer-review publications. For abstract and article submissions, various authorship formats are used, including A, B, and C for the XYZ Group, or the XYZ Group, and other permutations. For groups such as the CCCTG committed to the career development of new investigators, the listed author format helps to highlight the key roles that junior researchers play in multicenter projects. For each of these groups, authorship contributions must fulfill the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (57). The ANZICSCTG, ARDSnet, and the CCCTG each have an authorship policy document. None of these groups have moved exclusively to contributorship lists. All groups endorse informed consent and institutional review board disclosure (58).

## DISCUSSION

The goal of this article was to report on the development, organization, and operation of several groups throughout Europe, Australia, United States, and Canada who are conducting multicenter clinical research in critical care. We conclude that different models for research group infrastructure and management exist, as well as diverse approaches to the planning, funding, and conduct of individual studies. Nevertheless, several common features characterize these multicenter research groups; most prominent among them are a cohesive spirit, a sense of mission to achieve shared research goals, and acknowledgment that such an organization is much more than the sum of its parts. The success and productivity of several collaborative groups with limited resources demonstrate how academic motivation is not determined by research funding and how good ideas can be more important than money.

These groups have emerged during a period when clinical research in critical care has become increasingly rigorous (59), important, costly, and regulated. The research groups we discussed are organized to support different trials to varying degrees in different social and academic environments. Management methods are influenced by issues such as protocol complexity, research skills, group dynamics, leadership styles, and funding arrangements. Thus, one multicenter model may be exportable to some but not all groups or settings elsewhere.

Medicine is a microcosm of society. It is interesting to speculate whether the

**I**deally, the human and financial cost of critical illness, the funding required to conduct studies in the intensive care unit, and the potential benefit to society attained through these pursuits would be considered by policymakers who are allocating funds to biomedical research.

proximity of many European nations fostered or enhanced synergy among neighbors to achieve broader objectives. Perhaps due to the geographical dispersion, lower population density, and more modest research resources for investigators in Australia and Canada, open-membership groups have emerged in these countries with coast-to-coast representation. The formal organization and focused research program of ARDSnet illustrates what is possible when federal health policy promotes scientific excellence in critical care.

Challenges to conducting multicenter research include methodologic, statistical, and pragmatic issues. Methodologic issues addressed by these groups include defining criteria for the commencement and cessation of weaning and extubation and evaluating the influence of adjudication of major morbid outcomes on RCT results (60). Statistical issues addressed by these groups include development and analysis of novel outcomes (e.g., ventilator-free days) and time-dependent regression modeling to understand the differing influence of exposures before and during the ICU stay on clinical outcomes. Pragmatic issues include encouraging adherence to complex ventilator protocols and sustaining the commitment of many individuals to lengthy projects. Sharing data amicably and productively may be facilitated by guidelines for vetting, prioritizing, and interpreting analyses on shared databases. Future agendas include understanding the influence of health services organization and delivery on pa-

tient outcomes (61–63). Throughout this report, in addition to the challenges facing these research groups, we have highlighted strengths that might be viewed as different markers of success, including the clinical importance of the research, thematic nature of the research, multidisciplinary perspective of the research, number and quality of peer-review publications, commitment to career development in critical care, ability to secure and efficiently use research resources, and a combination of the foregoing.

There are several caveats to this report. Obviously, there is a great deal of clinically relevant, high-quality industry-initiated research and other investigator-initiated studies being conducted by individuals and groups not discussed herein. However, we elected to focus on investigator-initiated studies to better understand the processes that have emerged among a small, defined set of critical care research groups. Second, several active pediatric and neonatal critical care research groups exist that are not the focus of this report. Notably, the CCCTC has a growing number of pediatric investigators who are conducting four randomized trials in transfusion medicine, hypothermia for head injury, heliox for viral respiratory failure, and vasopressin for sepsis. Work on pediatric illness registries and health outcomes is also ongoing. Third, the research agendas for the groups we describe were determined largely by investigator interest and expertise; alternative methods for prioritizing have been reported recently; national intensive care research agenda setting was described for the United Kingdom (64). By using survey and nominal group techniques, Goldfrad et al. (65) found that the interests of senior physicians and nurses in 325 ICUs concentrated on the organizational aspects of practice (e.g., high-dependency care, nurse-to-patient ratios, and protocol evaluation) and management of organ system dysfunction (e.g., treatment of acute lung injury and acute renal failure). Fourth, a return-on-investment analysis of the multicenter research we described is beyond the scope of this report (66). It is clear that although high-quality, clinically relevant multicenter studies can be done by motivated experienced investigators with small budgets, some high-quality research can only be conducted with substantial research funding. Ideally, the human and financial cost of critical illness, the funding required to conduct studies

in the ICU, and the potential benefit to society attained through these pursuits would be considered by policymakers who are allocating funds to biomedical research.

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