Multisociety Task Force for Critical Care Research: Key issues and recommendations*

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Background: Research in critical care extends from the bench to the bedside, involving multiple departments, specialties, and funding organizations. Because of this diversity, it has been difficult for all stakeholders to collectively identify challenges and establish priorities.

Objective: To define a comprehensive agenda for critical care research using input from a broad range of stakeholders to serve as a blueprint for future initiatives.

Methods: The Critical Care Societies Collaborative (CCSC), consisting of the leadership of the American Association of Critical-Care Nurses (AACN), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM), joined the US Critical Illness and Injury Trials Group (USCIITG) in forming a task force to define a comprehensive critical care research agenda. This group of 25 identified experts was divided into subgroups to address basic, translational, clinical, implementation, and educational research. The subgroups met via conference calls, and the entire task force met in person for a 2-day session. The result was a detailed discussion of the research priorities that served as the basis for this report.

Results: The task force identified challenges, specific priority areas, and recommendations for process improvements to support critical care research. Additionally, four overarching themes emerged: 1) the traditional “silo-ed” approach to critical care research is counterproductive and should be modified; 2) an approach that more effectively links areas of research (i.e., basic and translational research, or clinical research and implementation) should be embraced; 3) future approaches to human research should account for disease complexity and patient heterogeneity; and 4) an enhanced infrastructure for critical care research is essential for future success.

Conclusions: This document contains the themes/recommendations developed by a large, multiprofessional cross section of critical care scientists, clinicians, and educators. It provides a unique framework for future research in critical care medicine. (Crit Care Med 2012; 40:254–260)

Critical care is one of the most rapidly growing areas in medicine. In the United States, care for the critically ill and injured consumes about $80 billion each year, an amount that constitutes approximately 1% of the gross domestic product (1). Mortality rates in intensive care units (ICUs) in US hospitals exceed those of all other care areas, with the result that one in five deaths in the United States occurs in the critical care setting (2). The best hope for both improving patient outcomes and containing costs lies in developing innovative treatments and systems of care, implementing new research findings, and identifying critical care research priorities.

The field of critical care medicine encompasses a broad spectrum of illness and injury and is practiced in a myriad of physical locations by providers with diverse skill sets. Research in critical care extends from the bench to the bedside, from classroom to the ICU, and from the community to the hospital. It involves many departments, specialties, professional societies and research institutes/foundations. Consequently, it has been difficult for experts representing the various communities and professional organizations to collectively identify challenges and establish priorities.

After conducting joint meetings for a number of years, in 2009 the four largest professional societies involved in critical care in the United States—the American Association of Critical-Care Nurses (AACN), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM)—formally established the Critical Care Societies Collaborative (CCSC) to explore common issues. At that time, in spite of the importance of critical care, there was no consensus on the research agenda in the United States. The closest approach was the 1995 report of the National Heart, Lung, and Blood Institute (NHLBI) Task Force on Critical Care Medicine. A 254-page consensus report was published in 1996, providing recommendations on the organization of clinical research in critical care. This report was updated in 2007, and guidelines for conducting clinical research in critical care were published in 2009. However, the CCSC recognized the need for a comprehensive critical care research agenda that would serve as a blueprint for future initiatives.

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For a comprehensive understanding of critical care research, experts from various organizations and stakeholders were brought together to address the challenges and opportunities in the field. The steering committee aimed to define a framework for critical care research and practice, identifying key characteristics and priorities.

### METHODS AND PROCESS

Each organization identified a key leader who served as a member of the task force steering committee. The steering committee convened via conference calls and face-to-face meetings to discuss and refine the framework. A successful agenda for critical care research and practice was defined by the five participating organizations, the steering committee, and input from leadership groups.

Within this framework, the steering committee developed a grid to define the spectrum of critical care research and practice based on input from a broad range of stakeholders. The resulting document would serve as a blueprint for future critical care initiatives, enabling targeted requests for applications issued by foundations, the National Institutes of Health (NIH), and other interested groups.

#### RESULTS

**Overarching Themes and Challenges to Critical Care Research**

All five subgroups believed that it is necessary to challenge the existing paradigms and basic assumptions underlying critical care research. While each subgroup examined the scope of priorities within its respective category of research, four key themes that limit the ability to conduct meaningful critical care research were identified (Table 2).

1. **Traditional “silo-ed” approach to critical care and research must be altered.**
2. **Suboptimal collaboration among investigators and funders.**
3. **Limited preclinical model systems, particularly among physicians by specialty training (e.g., medicine, surgery anesthesiology, pediatrics) may have stymied progress and innovation.**
4. **Altered.**

### Table 2. Comprehensive themes and challenges to critical care research

<table>
<thead>
<tr>
<th>Theme</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Traditional “silo-ed” approach to critical care and research must be altered.</td>
<td>This approach to research and practice often does not account for human factors or the effects of education.</td>
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<tr>
<td>2. Diverse areas of research need to be more effectively linked.</td>
<td>The diversity of research areas often does not align with the complexity of critical illness and injury and patient phenotypic heterogeneity.</td>
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<tr>
<td>3. Human research must account for the complexity of critical illness and injury and patient phenotypic heterogeneity.</td>
<td>The traditional methods of research must be expanded to consider the multifaceted nature of critical illness.</td>
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<tr>
<td>4. An enhanced infrastructure for clinical research is required.</td>
<td>The current infrastructure for clinical research is insufficient to support the needs of critical care research.</td>
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Crit Care Med 2012 Vol. 40, No. 1
Future Approaches to Human Research Must Account for the Complexity of Critical Illness and Injury and Patient Phenotypic Heterogeneity. Attempts to simplify human responses to easily described models have resulted in several problems. Important biological phenomena may go unrecognized. Focus on organ system-specific responses has obscured the importance of factors that provoke dysfunction in multiple organ systems and change the biological integration of systems that modulate normal organ-organ interaction. Objective definitions for the disorders and syndromes that comprise critical illness are often lacking or flawed, and standardized approaches to patient care may be absent. As a result, large-scale trials may be underpowered and comparisons between studies become problematic.

An Enhanced Infrastructure for Critical Care Research Is Required. Currently, critical care research is limited by a relative paucity of shared resources (such as databases and repositories) and the scarcity of independent, multicenter trial networks. Furthermore, success requires a coherent plan to develop the future research workforce and adequate funding.

**Recommendations for Specific Priority Areas for Research**

**General Principles (Table 3).** Investigation into several fundamental principles was deemed to be a priority across all critical care research domains.

**Definition/Clarification (“Unpacking”) of Critical Illness.** Although once based on hospital geography and the use of technologically advanced equipment, the terms critical illness and critical care now are broadly applied to conditions and treatment approaches. Critically ill patients ultimately develop a common syndrome of pathophysiologic derangement and organ dysfunction. We now know that the “final common pathway” hypothesis is likely too simplistic. Attempts to categorize critical illness into specific syndromes (e.g., acute lung injury [ALI], sepsis, trauma) have been unsuccessful, resulting in entities too broad, complex, and heterogeneous to be useful. A more refined approach is needed. Critical care research must focus on the responses of individual patients as their unique characteristics may dramatically affect outcome after insults and the response to interventions. This mandates a more complete understanding of the complex interactions among patients, comorbid conditions, insults, environment, and interventions.

To further address heterogeneity, refinement of animal models and extensive segregation of trial subjects into groups by specific characteristics will be necessary. Examples include: 1) segregation of patients based on etiology (e.g., ALI/acute respiratory distress syndrome in trauma vs. sepsis; ventilator-associated methicillin-resistant *Staphylococcus aureus* pneumonia vs. community-acquired pneumococcal disease); 2) separation of the basis of specific syndrome characteristics (e.g., specific electroencephalographic changes vs. coma); 3) incorporation and identification of patients with predominant comorbidities (e.g., alcohol-related disease, diabetes mellitus, coronary artery disease); and 4) stratification of adult patients on the basis of age and sex. Consideration should also be given to patient genotype and ecotype (e.g., type O blood, African Americans, inner-city patients). In all of these cases, both epidemiologic and experimental data suggest disparate responses.

**Investigation of Biomarkers, Including Proteins, Metabolites, RNA and DNA.** Biological markers have provided new insights into the pathophysiology and pathogenesis of critical care syndromes such as sepsis, ALI, and cardiac disease. In addition, they may provide a mechanism for tracking the course of these disorders. The repertoire of available biomarkers must be increased to: type subsets of patients and serve as research end points; incorporate testing of genetic influences via candidate gene strategies and genome-wide association studies; utilize gene expression studies via screening of RNA production or proteomics; and expand research to include metabolites and epigenomics.

New biomarkers must be validated against current approaches, such as standardized clinical prognostic scores based on physiology. The results should be rigorously compared to actual outcome data. Finally, most biomarker studies have focused on the initial inflammatory response. Markers heralding the onset of the chronic or recovery phases are required. Expansion of the investigation of biomarkers should include novel areas (e.g., imaging) and should focus more specifically on timing, cell type, and location rather than on circulation levels. Efforts should be made to identify markers that can be measured in both preclinical and clinical settings and to determine whether markers are reflecting helpful or deleterious responses to injury.

**Improvement in Models of Critical Illness.** Preclinical studies are often approached through use of animal models. However, illnesses that affect critically ill patients, such as sepsis and ALI, are difficult to model in the preclinical setting, in part because the models do not mimic the patient’s possible co-morbidities. Thus, more appropriate animal models that clarify the limitations of these surrogates must be developed. In addition, alternative approaches to preclinical testing are required. These approaches should include mathematical and computational biological techniques, computer modeling and application of techniques from other scientific disciplines and the social sciences. Finally, the phenotype of clinical illnesses can be enriched with information about the biology of the disorders and, conversely, the biology can be enriched by better phenotyping.

**Enhancing Access to Patients, Samples, and Data.** Current approaches to identifying patients, sharing information, and accessing biological substrates are inadequate. Future success in critical care investigation will require leveraging of existing research networks, tissue/sample banks, and databases. In addition, the development of national networks to facilitate research within the critical care community, within the global scientific establishment, and with social scientists.

### Table 3. Key research priorities for critical care: General principles

<table>
<thead>
<tr>
<th>Priority Area</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. “Unpack” critical illness: classify and separate clinical entities.</td>
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<tr>
<td>2. Identify and test novel biomarkers including protein markers, metabolites, RNA, and DNA.</td>
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<tr>
<td>3. Develop better models of critical illness and incorporate novel approaches in bench research to account for variations in patients, care strategies, and therapeutic interventions.</td>
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<tr>
<td>4. Enhance access to clinical research data.</td>
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<tr>
<td>5. Integrate new areas of research, scientific disciplines, and technology into the study of critical illness.</td>
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<tr>
<td>6. Develop and apply rigorous methodology to basic, clinical, health services, and translational research experimental design and to the evaluation of evidence.</td>
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will become increasingly important. Uniform access to networks can increase participation in clinical trials, enhance the use of human samples, and provide a more complete understanding of the effects of patient and disease heterogeneity. All three processes must be refined to capture information essential to critical care research.

**Application of New and Emerging Technology.** Several promising approaches may contribute to the development of innovative therapies in critical care. These include stem cells, beneficial microbes, pharmaconutrients, genetic modulators, nanotechnology, and improved tissue and organ engineering.

**Application of Rigorous Methodology.** Study design has taken many forms, from randomized controlled trials to observational reports. Comparison of these investigations often is hampered by differences in design, definitions, enrollment criteria, and timing. In addition, evaluation of research evidence suffers from lack of a uniform approach. Development and application of specific, predetermined methodologies to the conduct of the full spectrum of critical care research (bench, translational, clinical, outcomes, health services, education) will enhance cooperation and increase the power of results. Clearly defined rules for evaluation of critical care research will increase translation and dissemination into clinical practice.

### Basic Science/Cellular Research (Table 4)

**Initiation Of/Transition to Critical Illness.** Pathologic changes most often can be addressed and reversed before the patient requires intensive use of resources; however, some individuals progress to the severe, usually persistent, physiologic and metabolic derangements that we refer to as *critical illness*. This suggests a need to determine and differentiate extrinsic and host factors that alter the response to an initial insult and mediate progression toward “critical illness.”

**The Host Response.** A better understanding of critical illness requires determination of how its initiation and progression alters organ-specific and organism-wide host responses. Further insight into the mechanisms that produce cellular quiescence and isolation during critical illness, the role of cellular re-programming/de-differentiation, and the effects of critical illness on communication among cells, tissues, and organ systems will be essential. Finally, investigations should focus on the timing and sequence of factors that advance critical illness so that this information can be used to develop ways to halt or reverse this progression.

**The Microbiome.** While our understanding of microbiology has increased exponentially, its application to care of the critically ill has lagged. Therefore, it will be important to define the microbial ecology (or *microbiome*) in critically ill patients and to differentiate it from that found in patients who are not critically ill. Studies should include, but not be limited to, all types of bacteria, viruses, fungi, and parasites. Additionally, the microbiome is likely to change over time and may be affected by the etiology of injury, progression of a given syndrome, and specific host factors (e.g., comorbidities and environment; treatment effects, especially antibiotic use). Therefore, a better description of these changes is required, as is delineation of interactions among the microbiome, the host, and the innate and adaptive immune systems. Finally, and perhaps most importantly, it is imperative that we develop rapid, sensitive, specific, and cost-effective tools for microbiological diagnosis other than cultures.

**Modulation of Repair.** Our understanding of the mechanisms underlying repair of injured cells, tissues, and organs is rudimentary and limits the use of innovative therapy. Improving the care of the critically ill will require insight into the factors that modulate repair and investigation of the use of novel therapies (e.g., stem cells, beneficial microbes, pharmaconutrients, genetic modulators, and nanotechnology).

### Translational Research (Table 5)

**Integration of Mechanism and Novel Intervention.** Use of promising new basic/cellular approaches may provide innovative therapies, but application will depend on a well-planned integration of the new technology with detailed hypotheses. This will require the use of consistent specific outcome measurements across the biological scale, first in preclinical studies and then in clinical trials. In addition, the application of new technology may be dependent on a genetic predisposition to certain complications. Translation into clinical trials will necessitate national support for preclinical toxicity, safety testing and pilot studies, as well as the identification of reasonable comparison groups.

**Standardization of Study Design/Account for Effects of Disease Management.** To maximize the opportunity for rigorous and controlled translational research, preclinical trials must be optimally designed and should include control of process-of-care variables and predetermination of the effects of disease management apart from the new therapy being tested. This will ensure that approaches can be streamlined and protocols clearly understood. Clinically meaningful outcomes should be identified, developed, and tested in the preclinical setting. In addition to changes in traditional outcome variables (e.g., mortality, length of stay), changes in pathobiology should also be considered.

### Clinical Research (Table 6)

**Factors Preceding ICU Admission.** There is a paucity of clinical studies that focus on care delivered before ICU admission (prehospital, emergency department, operating room). Thus, methods
must be developed for the rapid, early recognition of acute, severely ill or injured patients who are at high risk for imminent deterioration. Early identification of individuals appropriate for clinical trials will enhance recruitment and potentially prevent progression to critical illness.

Acute Organ Support. A major concern in the treatment of critically ill patients involves the need for better acute organ support. In particular, the development of minimally invasive, biocompatible organ support is essential. New approaches must be tested and compared to meaningful outcome parameters.

Neuro-Inflammation. Future research should be directed at extending current attempts at therapeutic manipulation of the neuro-inflammatory state beyond steroids, nonsteroidal anti-inflammatory agents, and hormones.

Sedation. Sedation is used to promote psychological comfort, patient safety, and optimal use of therapies. However, drugs that alter consciousness clearly affect aspects of organ function/dysfunction and create conditions (e.g., myopathy, posttraumatic stress disorder, neurocognitive dysfunction, and delirium) that add to the pathobiology of critical illness. Therapeutic methods for enhancing patient comfort while reducing the need to manipulate consciousness are needed.

Reanimation. Clinically accessible approaches that accelerate global system and organ recovery/reanimation must be developed.

End-of-life Care. Research into the most appropriate ways in which to confront an inevitable final outcome in the critically ill has been neglected. A multicomponent educational and implementation strategy could minimize adverse consequences of end-of-life decisions and care.

**Health Services and Delivery Research (Table 7)**

Areas for investigation include the identification of appropriate methods and measures—as well as innovative ways to use technology—to conduct, analyze, and report research focused on improving the quality and safety of patient care, and patient and family outcomes.

Identification of Variables. Process factors, outcome measures, structural and organizational variables, and improvement strategies for palliative and end-of-life care must be pinpointed across the continuum of critical care, through the acute and chronic stages and into recovery. Areas for study should also include analysis and improvement of inter-professional team and team-family communication, related decision making, and the development of feasible, valid, and reproducible performance metrics and improvement processes.

### Table 6. Key research priorities for critical care: Clinical research

<table>
<thead>
<tr>
<th>Priority</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Develop methods for the rapid, early recognition of acute, severe disease in patients at high risk for imminent deterioration.</td>
</tr>
<tr>
<td>2.</td>
<td>Develop minimally invasive, biocompatible organ support.</td>
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<tr>
<td>3.</td>
<td>Focus on therapeutic manipulation of the neuro-inflammatory state.</td>
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<tr>
<td>4.</td>
<td>Explore new approaches that enhance patient comfort while reducing the need to manipulate consciousness.</td>
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<tr>
<td>5.</td>
<td>Develop clinically accessible approaches to accelerate global system and organ recovery/reanimation.</td>
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<tr>
<td>6.</td>
<td>Identify the best process and outcome measurements for critical illness research and palliative and end-of-life care.</td>
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### Table 7. Key research priorities for critical care: Health service and delivery research

<table>
<thead>
<tr>
<th>Priority</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Identify variables that affect outcomes and develop meaningful and reproducible performance metrics and improvement processes.</td>
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<tr>
<td>2.</td>
<td>Identify strategies to improve communication and coordination of care delivery.</td>
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<tr>
<td>3.</td>
<td>Determine those tools, processes, and programs (e.g., checklists and multidisciplinary rounds) that most effectively promote knowledge transfer and implementation.</td>
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<td>4.</td>
<td>Examine factors related to establishing a positive learning environment (e.g., technological advances, minimizing cognitive overload, and avoidance of burnout).</td>
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<tr>
<td>5.</td>
<td>Examine strategies for preventing errors and facilitating error reporting, and assess the effects on patient outcomes.</td>
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<td>6.</td>
<td>Examine the effectiveness of interventions to measure and treat prevalent/distressing patient symptoms (e.g., pain, fatigue, confusion/delirium) and family symptoms (e.g., anxiety, depression, stress disorders).</td>
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value and effective use in learning in the ICU. Areas for investigation should include the effects of simulation on patient risk, acquisition of expertise, and procedural competency. Elements to be studied are frequency of activity and both spontaneous and deliberate practice of individual components of care delivery. Approaches afforded by solo intervention and team involvement must be investigated and technological advances examined before they are incorporated into routine use. The value of applying simulation to unusual, common, and critical events is unknown and merits evaluation, as does the efficacy of simulation on competency assessment and retention of learning. Finally, cost-effectiveness and dissemination must be compared to the value of nonsimulation-based learning techniques.

**Team-Based Learning.** Critical care requires a team of providers, but approaches to team-based learning are lacking. It will be important to determine whether wide application of team-based learning and resource management is viable and valuable, and if so, identify which scenarios—rare, high-risk, or routine—benefit most. Identification of core elements of human performance (e.g., team leadership, adaptability, mutual trust, closed-loop communication) will differentiate high-performance from low-performance ICU management.

**Recommendations for Process Improvements to Support Critical Care Research**

The subgroups identified several opportunities to improve processes for effective critical care research. At its core, this research depends upon the elucidation of the timing, sequence, and duration of molecular and cellular events and the development of treatments capable of halting or reversing them. This requires development of novel experimental models, assessment of the impact of maturation and aging on pathobiology, understanding of the effect of different systems and structure of care on patient outcomes, and comprehension of regional differences in outcomes. These present substantial challenges. At the core is a need for improved interaction and communication within and among research institutions and entities.

**Research Environment.** To fully engage in critical care research, individual facilities will need to develop a robust infrastructure (laboratory space, technical support personnel, information technology equipment, and user-friendly databases) and close cooperation among clinical entities and among basic, translational, clinical and health services scientists, both within and across departments/divisions. This should further enhance the ability to perform small, hypothesis-generating (pilot) trials that require a limited number of patients. Despite a number of prominent success stories in critical care research, interdisciplinary research collaboration has been inadequate.

**Preclinical Modeling.** Critical care encompasses a wide scope and severity of clinical conditions, as well as a variable duration of illness, not fully reflected in current models. Further interdisciplinary collaboration will be required if experimental modeling is to facilitate a bench-to-bedside-to-community research program. One of the essential components of preclinical modeling can be provided by individuals well-versed in complex database development and manipulation, mathematical modeling, and multi-level and clustered statistical analyses. This will allow for prospectively designed trials that more completely capture essential data.

**Patient Characteristics.** Critical care medicine involves a heterogeneous patient population. Better characterization of both individual patients and patient cohorts could lead to an improved understanding of the pathogenesis of injury and illness allowing for more targeted interventions and improved outcomes.

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**Table 8.** Key research priorities for critical care: Education research

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<tr>
<th>Priority</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Incorporate cognitive psychology, systems engineering, and social science into critical care education and training.</td>
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<tr>
<td>2.</td>
<td>Determine the relative importance of key elements such as team interactions, deliberate practice, assessment, and debriefing in simulation.</td>
</tr>
<tr>
<td>3.</td>
<td>Refine team-based learning, including examining differences between high-performing and low-performing units, and determining in which scenarios team-based learning has the greatest value.</td>
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**Regulatory Challenges.** Critical illness most often involves patients who cannot provide informed consent. Attempts to obtain permission to enroll individuals in investigations may appear inadequate to patient surrogates. The emergency exception from informed consent for resuscitation research (21CFR §50.24) (5) was created to circumvent these challenges, but implementation is fraught with difficulties, such as a burdensome consent process, the need for community consultation, a lack of local institutional review board (IRB) familiarity with exemption implementation, preemptive local and state laws, a perception that nonresearch entities (emergency medical services agencies, community hospitals, nursing homes) are precluded from participation. Further, this exemption applies only to acute care and resuscitation and not to the remaining spectrum of critical illness. These problems mandate a comprehensive approach to enhancing enrollment into critical care trials. This might involve uniform approaches to consent or common IRBs with extended jurisdiction. Any proposed solution should incorporate input from individuals with expertise in the legal, governmental, and societal ramifications of investigation in compromised populations.

**Research Networks.** Multidisciplinary networks provide essential infrastructure and project support for clinical trials and outcome-oriented research. As such, they improve access to patients, enhance recruitment, and simplify implementation. Researchers can capitalize on the combined resources of member institutions and focus on the rapid translation of promising scientific knowledge into clinical advances. However, the development of appropriate research networks is complicated. Data transmission can be hampered by security issues, liability concerns, and differing philosophies among individual IRBs. Comprehensive solutions, such as the creation of a central IRB that frees local boards to decide local issues, are required as part of a long-term solution. A reasonable beginning would be the expansion of existing networks and establishment of a virtual network that can respond rapidly to new and unique challenges (e.g., pandemic flu).

**Standardization of Approach.** A uniform approach to research implementation would be invaluable to the appropriate design, review, and conduct of critical care investigations. Such a template would address key issues in patient iden-
tification, consent and enrollment, disease characterization, specialized care settings, special populations, co-morbidities, and study methodology.

**Funding.** Traditionally, funding streams have been aligned on disease- or age-specific criteria. Critical care research inherently crosses these boundaries. Retooling the current approach could enhance coordination and collaboration across funding agencies and institutes to ensure adequate support for critical care investigations.

**Flexibility.** Critical care research must move beyond traditional investigative approaches. Studies will need to incorporate economics (cost-effectiveness, efficient resource utilization), improvement science (decreasing errors), implementation science (translating knowledge into practice), social and behavior sciences (understanding variations in clinical practice), informatics, and bioengineering.

**CONCLUSIONS**

The increasing demand for resources to address outcome challenges mandates enhanced investment in critical care research. We have outlined a series of recommendations to facilitate research progress across the spectrum of critical care. Dynamic, broad-based strategic planning will be necessary to maintain and adjust research priorities as knowledge advances. Our recommendations necessitate new initiatives, periodically re-structured and renewed national research priorities, and enhanced cooperation throughout the critical care community and among all stakeholders.

**REFERENCES**


**APPENDIX**

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