CHEST

Ahead of the Curve

United States Critical Illness and Injury Trials Group

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The United States Critical Illness and Injury Trials (USCIIT) Group is an inclusive, grassroots "network of networks" with the dual missions of fostering investigator-initiated hypothesis testing and developing recommendations for strategic plans at a national level. The USCIIT Group's transformational approach enlists multidisciplinary investigative teams across institutions, critical illness and injury professional organizations, federal agencies that fund clinical and translational research, and industry partners. The USCIIT Group is endorsed by all major critical illness and injury professional organizations spanning the specialties of anesthesiology, emergency medicine, internal medicine, neurology, nursing, pediatrics, pharmacy and nutrition, surgery and trauma, and respiratory and physical therapy. Recent successes provide the opportunity to significantly increase the dialogue necessary to advance clinical and translational research on behalf of our community. More than 200 investigators are now involved across > 30 academic and community hospitals. Collectively, USCIIT Group investigators have enrolled > 10,000 patients from academic and community hospitals in studies during the last 3 years. To keep our readership "ahead of the curve," this article provides a vision for critical illness and injury research based on (1) programmatic organization of large-scale, multicentered collaborative studies and (2) annual strategic planning at a national scale across disciplines and stakeholders.

CHEST 2013; 143(3):808–813

Abbreviations: CCSC = Critical Care Societies Collaborative; CTSA = Clinical and Translational Science Award; LIPS = Lung Injury Prevention Study; NCAT = National Center for Advancing Translational Science; NIH = National Institutes of Health; OECR = Office of Emergency Care Research; PROOF = Program for Prevention of Organ Failures; USCIIT = United States Critical Illness and Injury Trials

The United States Critical Illness and Injury Trials (USCIIT) Group created clinical research infrastructure to reduce the barriers to investigation for the critical illness and injury communities in the United States.[1]

As an inclusive, grassroots "network of networks," the USCIIT Group's dual missions are to foster investigator-initiated hypothesis testing and to develop recommendations for strategic plans at a national level.[2] The USCIIT Group was funded in 2008 by a National Institutes of Health (NIH) (National Institute of General Medical Science) meeting grant (U13) with four aims[3]:

1. Establish an inclusive, nationwide network of experts to review published data, vet hypotheses, write clinical protocols, and generate pilot data that facilitate implementation of large clinical trials.

Manuscript received September 17, 2012; revision accepted September 18, 2012.

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Funding/Support: This work was funded in part by the National Institutes of Health [Grants U13 GM083407, U01 HL108712] and the US Department of Health and Human Services [Contract HHSOl 0020 ll00062P].

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DOI: 10.1378/chest.12-2287

2. Promote interactions and synergy across established research programs, both academic and nonacademic, to improve the robustness of clinical trials and test hypotheses in a US population.
3. Provide a venue to discuss education and training in the science of clinical trial design, conduct, analysis, and reporting for critically ill or injured patients.
4. Ensure patient protection and privacy by addressing the ethical, legal, and social implications of research in the specialized circumstance of critical illness or injury.

To these ends, the USCIIT Group provides a biweekly teleconference venue for investigator and NIH interinstitute communications; engages in a multisociety task force for annual research strategic planning; catalyzes Health and Human Services interagency dialogue for endorsement of transforming initiatives; seeks to coordinate research training nationally as a Clinical and Translational Science Award (CTSA) Thematic Special Interest Group; and fosters innovative, multidisciplinary, multicenter studies that typically start as investigator-driven clinical proposals. Typically, hypotheses are tested by multidisciplinary teams that openly solicit input and encourage collaboration among investigators with similar interests across institutions. The USCIIT Group is governed by a steering committee of investigators and by an organizing committee composed primarily of Health and Human Services staff. The USCIIT Group involves >200 investigators across >30 academic and community hospitals. Collectively, USCIIT Group investigators have enrolled $>10{,}000$ patients from academic and community hospitals in studies during the last 3 years.[4,5]

Significance

The USCIIT Group is endorsed by all major critical illness and injury professional organizations spanning the specialties of anesthesiology, emergency medicine, internal medicine, neurology, nursing, pediatrics, pharmacy and nutrition, surgery and trauma, and respiratory and physical therapy. The transformative nature of the USCIIT Group and its unique role in the United States have been recognized.[6] The group plays an important role, as there is no federal agency or national organization in the United States that facilitates critical illness and injury research or strategic planning across specialties and the human developmental continuum. The USCIIT Group Thematic Special Interest Group also provides a new opportunity to leverage the huge investment in infrastructure across 60 academic sites (nodes) in the CTSA network. Finally, the USCIIT Group provides a network for the new era of health services and comparative effectiveness research, as described recently by the leadership of the NIH, the Agency for Healthcare Research and Quality, and the new Patient-Centered Outcomes Research Institute.[7,8] A spectrum of important deliverables is expected, including, but not limited to, the following:

- Create of a "network of networks" for critical illness and injury research for rapid data sharing, analysis, and reporting, leveraging the existing research infrastructure across 60 sites in the CTSA network.
- Efficiently conduct (in terms of recruitment and funding spent) multicentered studies, the results of which lead to optimized outcomes and reduce unwanted practice variance.
- Coordinate peer review for research protocol generation and presentation of consensus policies, procedures, results, and recommendations.
- Harmonize institutional review board submissions, working with national organizations such as the Public Health Ethical Research Review Board.
- Organize research education and training across the 60 sites supported by the NIH CTSAs.
- Facilitate communication and create infrastructure to promote national emergency preparedness.
- Establish biobanks linked to robust clinical databases that can be used to identify biomarkers and genetic variation associated with outcome.

Finally, to address its missions globally, the USCIIT Group participates in the International Form of Acute Care Trialists (InFACT), a collaborative network of investigator-led research groups.[9]

Vision

The USCIIT Group's collaborative approach enlists multidisciplinary investigative teams across institutions, critical illness and injury professional organizations, federal agencies that fund clinical and translational research, and industry partners. Recent successes provide the opportunity to significantly increase the dialogue necessary to advance clinical and translational research on behalf of our community. Operationally, this will depend upon leveraging resources available through the new CTSA Thematic Special Interest Group (NIH National Center for Advancing Translational Science; NCATS) and improved coordination of strategic planning with the Critical Care Societies Collaborative (American Association of Critical Care Nurses, American College of Chest Physicians, American Thoracic Society, and Society of Critical Care Medicine).

Investigator-Initiated Hypothesis Testing

The foundation of the USCIIT Group's hypothesis-testing enterprise is the interest of an individual investigator to present a clinical proposal that tests a hypothesis, working in collaboration with a multidisciplinary, multi-institutional team. To date, >50 clinical proposals have been presented at USCIIT Group meetings, with most still in the design phase. Several have started enrollment, and a few have completed analysis and published results. The most mature of these USCIIT Group multidisciplinary programs have used these results as preliminary data to support federally funded, large, multi-institutional studies. As the USCIIT Group evolves, we expect that this hypothesis-testing pathway will increase in throughput. Several examples of programmatic development are provided here.

Program for Prevention of Organ Failures: Efforts to prevent organ failure are hampered by three barriers: (1) compartmentalization of care (ED, operating room, ICU, and so forth); (2) the difficulty of identifying early those at risk; and (3) lack of proven, effective treatments. Building on the success of the Lung Injury Prevention Study (USCIITG-LIPS),[4,10] the unique, multidisciplinary, USCIIT Group network, and CTSA-funded infrastructure, USCIITG-Program for Prevention of Organ Failures (USCIITG-PROOF) will address all three barriers simultaneously through rapid-cycle, multicenter clinical trials that span clinical domains to test a variety of interventions that prevent organ failure in those at risk. USCIITG-PROOF investigators currently are working on multiple projects aimed at the prevention of acute lung injury, including LIPS-Aspirin (LIPS-A) (a National Heart, Lung, and Blood Institute-funded multicenter trial to investigate the usefulness of aspirin to prevent acute lung injury) and LIPS-B, an investigator-initiated study to examine whether budesonide and the β-agonist formoterol can prevent acute lung injury in high-risk patients. Additionally, USCIITG-PROOF will advance the methodology used to conduct clinical trials, moving away from existing manual data collection techniques toward automated extraction of clinical data from electronic medical records. The first test of this technology will come from a Centers for Medicare and Medicaid Services-sponsored, multicenter innovation award with USCIIT Group investigators and Philips Research North America. The goal of this project is to determine whether a novel acute care interface, Patient-Centered Cloud-Based Electronic System-Ambient Warning and Response Evaluation (ProCCESs AWARE), can reduce preventable errors in the ICU, improve outcomes, and reduce costs and, in the process, train >1,400 providers to use state-of-the-art acute care informatics.[11] ProCCESs AWARE aims to facilitate care in the ICU with built-in tools for best practice compliance, practice surveillance, decision support, and reporting.

Program for Critical Illness Outcomes: Care delivered in ICUs is high intensity and high cost and has remarkable variation in use and outcomes. Variations have been described with individual features such as geographic locale, ICU and provider specialization, and patient acute disease and illness severity, among other factors. To date, little is known about which ICU organizational and structural factors are associated with high-quality care and optimal patient outcomes. To determine which of these factors are associated with high-quality critical care and relevant clinical outcomes, USCIITG-Program for Critical Illness Outcomes (USCIITG-CIOS) has collected both ICU-specific and patient-specific data on >6,000 patients from >60 US ICUs.[5] This first-outcomes study found substantial variation in protocol availability and use—with the majority of ICUs having ≥16 protocols in place—and patient mortality was noted to vary according to ICU type (medical vs surgical vs mixed). In future outcomes studies, USCIITG-CIOS will increase our understanding of the relationship between multiprofessional ICU staffing, care pathway and protocol use, and patient-centered clinical outcomes. In so doing, it permits testing a number of new methods of optimizing ICU patient care, both at the patient level (which patients, when, and how best to deliver the care) and institutional level (staffing, protocols and pathways, and so forth). This will identify hypotheses to test in novel effectiveness trials at the regional, state, and national levels.

Program for Emergency Preparedness: National emergencies over the past decade demonstrated that the US federal emergency response system had insufficient capabilities to rapidly collect clinical data to inform decision-makers and key end-users in public health emergencies. In particular, physiologic patient data are needed to provide immediate insight into the impact of the event on critical health-care resources and to identify groups with high risk for morbidity and mortality. The USCIIT Group Program for Emergency Preparedness (USCIITG-PREP) aims to significantly enhance the national capability to rapidly glean crucial information regarding the clinical course of acute illness and injury and guide clinical resource requirements during emergent events. Working with leading professional organizations and the Homeland Security Information Network, USCIITG-PREP will develop mechanisms for rapid data collection, analysis, and dissemination of findings during public health emergencies. Pre-event work on protocols, data collection processes, rapid analysis techniques, and means to quickly disseminate findings to stakeholders are all

crucial to making clinical science networks effective at enhancing the response. The USCIIT Group will leverage existing infrastructure to both strengthen pre-event operational science capabilities and provide timely data and situational awareness across the emergency-care continuum during public health emergencies.

Program for Early ICU Rehabilitation: Physiatrists, physical therapists, respiratory therapists, speech-language pathologists, and occupational therapists are essential for coordinating rehabilitation of critically ill or injured patients. Early rehabilitation can help to ameliorate and even avoid severe deconditioning associated with post-ICU syndrome, which presents as long-term physical, cognitive, and mental health problems after severe critical illness or injury.[12-14] USCIITG Program for Early ICU Rehabilitation (USCIITG-PEIR) seeks to identify areas of heterogeneity of care and to improve early rehabilitation for critically ill or injured patients. USCIITG-PEIR soon will launch a multicenter, randomized controlled clinical trial to measure the effect of early rehabilitation on hospital stay, muscle loss, and functional outcomes in burn patients with acute respiratory failure. In addition, a "point in time" observation study will be conducted to sample current rehabilitation strategies among ICUs nationally.

CTSA Thematic Special Interest Group: As an additional approach to accelerate progress in our field, the USCIIT Group will leverage the resources of the NIH CTSAs, now funded by the NCATS. Since 2006, CTSAs have supported leading US academic research centers to create infrastructure for translational research, to promote the training and career development of clinical and translational researchers, to develop innovative methods and technologies that strengthen translational research, and to create local core resources through a national dialogue of shared practice.[15] The recent creation of CTSA Thematic Special Interest Groups provides the opportunity for investigators to leverage the extraordinary resources the 60 CTSA sites provide in aggregate, in effect creating a 60-node national research network for phenotypic-specific ("thematic") research. CTSA collaborative expertise is available for drug discovery; statistics; clinical epidemiology; trial design; prevention and personalized medicine; public-private partnerships; ethics and regulatory affairs; research education, training, and career development; comparative effectiveness research; and health services research. The USCIITG-Thematic Special Interest Group (USCIITG-TSIG) will expand the scope and impact of USCIIT Group operations, working in partnership with investigators located at these 60 CTSA-funded research centers. Consistent with our recently published research agenda and the NCATS mission, we will create a consensus strategic plan for advanced informatics, education and training, and multicenter clinical trials that leverages regional and national CTSA infrastructure.

Other Programs: In addition to these broader areas, there are a number of other programs for targeted disease states, such as burn injury and trauma, currently in development. In other words, we expect over time that the number of USCIIT Group programs will increase, consistent with the USCIIT Group's dual missions and the strategic imperatives described in our recently published national research agenda (see the following). For example, a new program to optimize tracheostomy practice seeks to address variance in practice (including timing of procedure and technical approach), determine which patient populations (if any) benefit from earlier tracheostomy, identify metrics for patient-centric outcomes, and optimize post-tracheostomy management.[16]

Strategic Planning

The USCIIT Group has been at the forefront of recent efforts to identify and address key areas in critical illness and injury research, as articulated by investigators, professional organizations, funding agencies, and regulators. For instance, the USCIIT Group annual meetings have served as an interdisciplinary forum for dialogues among key critical illness and injury research stakeholders, including federal funding agencies, professional organizations, and regulatory agencies. More information and the broad array of session topics and speakers from previous and future meetings can be found on the USCIIT Group website.[3]

New Alliance for Critical Illness and Injury Research: As part of this "new alliance,"[1,6] the USCIIT Group worked with the Critical Care Societies Collaborative (CCSC) to lead the development of a comprehensive, strategic research agenda for critical illness and injury. Funded by the National Heart, Lung, and Blood Institute, a 2-day, multicare setting, multidisciplinary meeting was held, the conclusions of which were published simultaneously by the official organs of the CCSC organizations.[17-20] This CCSC-USCIIT Group report delineated challenges, specific priority areas, and recommendations for improvements in critical care research infrastructure and processes. For example, four overarching themes were identified: modify the "silo-ed" approach to critical care research; embrace linkage of basic, clinical, and translational research; account for disease complexity and patient heterogeneity; and enhance critical care research infrastructure.[17-20] The report also emphasizes that continued,

broad-based, strategic planning will be necessary to maintain and adjust research priorities as knowledge advances; the vision is to revise and refresh this national research agenda on a regular basis, perhaps biannually.

Office of Emergency Care Research: The need for a dedicated centralized office at the NIH for emergency care research was recognized in the 2007 Institute of Medicine Report on Emergency Care.[21] Emergency care research frequently studies highly dynamic, multiorgan pathophysiology in patients with undifferentiated signs and symptoms. This type of research inherently intersects multiple organ-specific and population-specific missions of the individual institutes and centers at the NIH.[22,23] Research funding streams were found to be inadequate and frequently aligned across disease-specific boundaries that were minimally relevant in the emergency care setting.[23] The Institute of Medicine Report recommended an examination of the opportunities in emergency and trauma care research that in turn would motivate creation of a strategy to optimally organize and fund the research.[21] This in turn led to roundtables, requests for information, and conferences to address how the NIH and the extramural community might best advance research in the emergency setting. Implementation of the recommendations culminated recently in the creation of a new NIH Office of Emergency Care Research (OECR).[24] The formation of the OECR is a groundbreaking advance not only for emergency care investigators and research but also for the new pathway it provides for expanded critical illness and injury research initiatives. The interdisciplinary, multicare setting and multiorgan system nature of critical illness and injury research can frequently run into the same type of funding stream hurdles that challenged emergency care research. We expect that the trans-NIH approach of OECR will provide a model to coordinate critical illness and injury research across the time and care setting continuum (prehospital to rehabilitation).

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Cobb is the Director, and Drs Cairns and Bhagwanjee are the Associate Directors, of the United States Critical Illness and Injury Trials (USCIIT) Group. Drs Cobb and Cairns are co-principal investigator of an NIH U13 award that supports the USCIIT Group [National Institutes of Health U13 GM083407]. Dr Cobb is also the principal investigator for a Department of Health and Human Services/Assistant Secretary for Preparedness and Response award that funds the USCIIT Group Program for Emergency Preparedness [HHS-OS74039]. Dr Cairns has also served as a consultant for bioMerieux. Drs Blum, Morris, Martin, Gong, and Bhagwanjee have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

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