Investigator-led clinical research consortia: The Canadian Critical Care Trials Group

John C. Marshall, MD, FRCSC, Deborah J. Cook, MD, MSc, FRCPC, for the Canadian Critical Care Trials Group

Advances in the care of critically ill patients are dependent upon rigorous clinical research undertaken to characterize natural history and risk factors, and determine optimal approaches to the management of the diseases of the critically ill patient. The Canadian Critical Care Trials Group (CCCTG) was formed in 1989 to foster such research. It has grown to become a national, multidisciplinary organization with more than 100 members, and more than 3 dozen active research programs. Its members have been highly successful in obtaining funding for, completing, and publishing well-designed studies that have informed international practice in areas such as transfusion, stress ulcer prophylaxis, long term outcomes from acute respiratory distress syndrome, diagnosis and management of infection in the intensive care unit, and end-of-life care. In the process, the CCCTG has developed a highly effective culture of scientific mentoring, and has served as a model for investigator-led critical care research groups around the world. This review summarizes the history, activities, approaches, and challenges of the CCCTG, in the conviction that investigator-led groups such as ours represent the future of intensive care unit-based research. (Crit Care Med 2009; 37[Suppl.]:S165–S172)

Key Words: critical care trials; research collaborations; investigator-led research

The Canadian Critical Care Trials Group (CCCTG) is the oldest investigator-driven clinical research consortium in the discipline of critical care. It has also been one of the most productive. Founded by a handful of academic intensivists in 1989, it has grown to a national organization of more than one hundred members – both physicians and nonphysicians – with an active research portfolio of more than 35 research programs. It has served as a model for similar groups in Australia and New Zealand, Sweden, and Scotland, and for new initiatives in Ireland, South Africa, the Middle East, and the United States.

Although investigator-led research consortia are well-established in oncology (1), they are a relative novelty in critical care, where industry-run trials still dominate the landscape of multicentered clinical research. This situation is changing, and there is a growing need to optimize the structure and enhance the influence of investigator-led groups. This overview of the history and tribulations of the CCCTG provides some subjective, but hopefully useful insights into the experience of one such group over the past two decades, synthesizing these into a series of lessons that may prove useful to others.

The Research Question

Research begins with a question. How the question is formulated shapes the subsequent research enterprise. Even more importantly, who poses it has a profound impact on how the enterprise evolves, where it will ultimately go, and whether it will reach that end.

Clinical research undertaken by industry is undertaken with the objective of bringing a new technology to market, and having done that, ensuring and expanding its commercial niche. Innovation arises in the technology under study, rather than in the methods by which it is studied, or the rigor with which they are applied to ensure the most reliable answer. The question is more than whether the technology works; rather the sponsor seeks to achieve regulatory approval, and to maximize the financial return associated with subsequent sales of the product. The design of the clinical research program, therefore, is strongly influenced by the requirements of regulatory agencies, and limited by the requirement that a commercially viable product emerge at the end.

The questions posed in investigator-led studies typically arise from either curiosity, on the one hand, or confusion and controversy on the other. Curiosity drives basic research to determine the structure of DNA, or to understand the processes through which healthcare workers come to make decisions regarding end-of-life care in critical illness (2). Confusion – the awareness that several plausible therapeutic options exist, and that clinicians are divided over which to use – spawns studies to determine optimal approaches to the resuscitation of the septic patient (3), to assess the relative merits of colloids and crystalloids (4), or to determine whether maintenance of normoglycemia will benefit the critically ill patient (5). Controversy for the clinician is reformatted as clinical equipoise for the investigator (6), and spurs a structured effort to resolve the uncertainty that breeds practice variability. For such studies, the ultimate conclusion is often less important than the reliability of the answer.

The research question addressed by investigator-led trials may be articulated collectively by the consortium or by the individual investigator. A collectively articulated research agenda enables a sys-

From the Department of Surgery, and the Interdepartmental Division of Critical Care Medicine, University of Toronto, and the Sepsis Research Laboratory, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada, and the CLARITY Research Group, McMaster University, Hamilton, Ontario, Canada.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, Email: marshallj@smh.toronto.on.ca

DOI: 10.1097/CCM.0b013e3181921079

tematic and iterative approach to advancing knowledge about the clinical management of a disease process. For example, the National Surgical Breast Adjuvant Project has undertaken a series of studies over the past three decades to determine the optimal management of women with breast cancer, addressing such questions as the extent of surgical therapy (7), and the need for adjuvant radiotherapy or chemotherapy. Specific research questions arise from the findings of previous studies, and are prioritized by the research collective. A similar approach has informed the research agenda of the National Institutes of Health-funded Acute Respiratory Distress Syndrome Network collaborative that studies the management of critically ill patients with acute respiratory distress syndrome (8, 9).

The CCCTG has adopted the alternate model, undertaking research programs that are brought forward by individual members, and that reflect their unique interests and passions. Our inaugural meeting in the spring of 1989 brought together about 10 academic intensivists to discuss the possibility of establishing a national network for investigator-initiated clinical research. Participants were invited to bring proposals for research projects. Three of the six proposals presented addressed the question of the risk of ventilator-associated pneumonia (VAP) resulting from the use of acid-reducing strategies for stress ulcer prophylaxis, and so we decided to undertake a trial, led by Dr. Deborah Cook, to determine whether stress ulcer prophylaxis with sucralfate would reduce the risk of pneumonia associated with the use of the histamine H2 blocker, ranitidine (10).

The advantages of an investigator-driven research agenda to a clinical research consortium are several. It is responsive to the needs and interests of the members of the research group and shaped over time by the most active members. The questions addressed reflect issues of contemporary interest to a community of practitioners, and the research portfolio changes over time as the dominant clinical issues change. It also tends to promote research questions that go beyond clinical management of a disease process to focus on the process of research itself. Finally, it is ideally suited to organizations such as the CCCTG that do not receive sustained core funding over time, but whose work is supported by grants for individual research projects. It has proven particularly important in developing a generic approach to clinical research that we term *programmatic research*, and that views research as an integrated approach to a clinical question, rather than as one, or even a series, of clinical trials.

Programmatic Research: The CCCTG Model

Having decided to focus on the risk of pneumonia associated with the use of H2 blockers for stress ulcer prophylaxis for its initial venture into collaborative multicenter research, the CCCTG faced the challenge of designing a protocol to address the question. That we would undertake a multicenter, blinded, randomized controlled trial was self-evident; however, key study design issues were immediately apparent. How would we define clinically important bleeding and VAP as the two primary outcome measures for the trial? And as importantly, there was a shared impression that rates of clinically important stress bleeding were decreasing: we lacked the basic epidemiologic information on incidence and risk factors that would enable us to identify an at-risk population to study and to estimate the size of study population necessary to answer our primary question. Thus we decided to undertake preliminary pilot studies to better inform the design of a definitive trial, including meta-analyses on the role of gastric pH in the etiology of VAP (11) and on the impact of stress ulcer prophylaxis on rates of bleeding (12), and a large observational study to determine the incidence of, and risk factors for, stress bleeding in contemporary Canadian intensive care units (ICUs) (13). A 1200 patient randomized controlled trial (RCT) comparing sucralfate with ranitidine (10) generated a series of secondary analyses of risk factors for clinically important gastrointestinal bleeding in mechanically ventilated patients (14), of the burden of illness of upper gastrointestinal bleeding (15) and VAP (16), and of the utility of invasive diagnostic techniques for VAP (17), that in turn, provided important pilot data for the design of a large RCT addressing the diagnosis and treatment of VAP (18) (Fig. 1).

We developed this model further within the context of a research program on transfusion of the critically ill. Led by Dr. Paul Hébert, the Transfusion Requirements in Critical Care (TRICC) program sought to determine optimal thresholds for transfusing stable, anemic critically ill patients. The design of an 838 patient multicenter RCT (19) was informed by preliminary studies that defined variability in transfusion practice using the methods of a scenario-based questionnaire (20) and an observational cohort study (21), and a 69-patient pilot study to evaluate recruitment feasibility and clinician compliance with the transfusion threshold (22).

As the CCCTG has matured, this programmatic research model has evolved to become the foundation of our approach to clinical research (2, 23). Programmatic research considers clinical research to be an integrated series of investigations, using a variety of complementary methodologies, to determine best practice in critical care, and to implement that knowledge to improve patient outcomes (Fig. 2).

A research program starts with a formal structured review of what is known about the research question through the performance of one or more systematic reviews or meta-analyses. Since our studies typically address the comparative efficacy of two or more available clinical strategies, it is of fundamental importance to quantify practice variability to establish that clinical equipoise exists, and to identify plausible approaches to compare in an RCT. Clinician attitudes can be probed through scenario-based questionnaires, while practice variability in the real world is best assessed through observational studies. For the TRICC trial, for example, transfusion thresholds of 70 g/L in the restrictive arm, and 100 g/L in the liberal arm were established on the basis of a scenario-based questionnaire and an observational study, and represented acceptable, but divergent transfusion thresholds with which clinicians would feel comfortable. For the Appropriate Antimicrobial Therapy in Critical Care (AATICC) program evaluating the utility of empirical antibiotics for patients thought to be at intermediate risk of having a nosocomial infection, a scenario-based study revealed striking divergence in the use of empirical antibiotics for three hypothetical patients with possible nosocomial infection (24), and so demonstrated that although individual clinicians have strongly held opinions, a state of community equipoise exists. Observational studies play an further role in characterizing the potential study population – determining the prevalence of

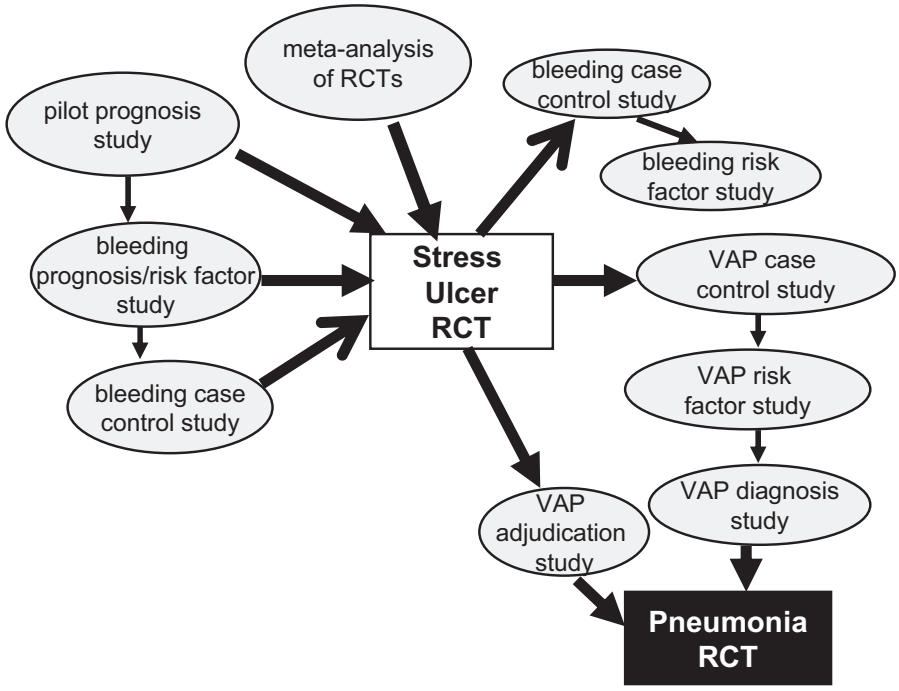

Figure 1. The Canadian Critical Care Trials Group Research Program in Stress Ulcer Prophylaxis. Having decided to address the question of whether ablation of gastric acidity during stress ulcer prophylaxis increases the risk of ventilator-associated pneumonia (*VAP*) as its first clinical study, the Canadian Critical Care Trials Group recognized that answering that question required an integrated series of studies to synthesize what was known, to establish the epidemiology of stress bleeding, and to achieve consensus on metrics and definitions. Our completed 1200-patient study spawned further work to look at the attributable costs of stress ulceration, and the diagnosis of VAP, and so set the stage for a second large randomized controlled trial (*RCT*) addressing the specific questions of the diagnosis and treatment of VAP.

and risk factors for a particular condition, and so facilitating estimates of recruitment rates, and ascertaining anticipated outcomes in the population of interest (23).

Pilot studies permit the investigator to evaluate the feasibility, acceptability, and compliance rates of a study protocol, and so increase confidence that a larger trial powered to assess clinical impact can be completed successfully. Clinical outcomes are of secondary importance. One can evaluate recruitment rates, assess the feasibility of an intervention, determine compliance with a protocol, evaluate whether blinding is effective, and evaluate tools for data collection and study monitoring. Pilot studies are also excellent platforms for determining clinician perspectives through the administration of questionnaires, for conducting biological studies to evaluate diagnostic biomarkers, or to use the systematic intervention of a clinical trial to address a biological question.

The randomized controlled trial is the centerpiece of any clinical research program. The inherent heterogeneity encountered among critically ill patients, and the relatively small effect size that any given intervention can plausibly be expected to achieve, dictate that definitive trials must be large, sometimes recruiting thousands of patients (4). These trials are expensive and complex: preliminary studies such as those described can facilitate their successful conduct. Inclusion and exclusion criteria can be more readily defined, and the feasibility of the planned intervention understood. Estimates of sample size and recruitment rates can be more reliable, and study teams can be created. Finally, granting agencies look favorably upon evidence that a study is well thought out and feasible.

The completion of a trial does not signal the end of a research program. To improve patient care, new knowledge must be adopted into practice, and so guidelines development and knowledge translation strategies represent the final elements of the programmatic research model. Inevitably the process of studying a question generates important new questions, and the cycle continues.

Structure and Operations

Membership in the CCCTG is open to healthcare workers with an interest in the care of the critically ill patient. We currently have approximately 100 members, including physicians, nurses, pharmacists, respiratory therapists, and trainees, and representing both adult and pediatric critical care. Members are self-funded, and membership fees for nonphysicians and trainees are reduced.

The activities of the CCCTG are coordinated by an Executive Committee consisting of a Chair, past-Chair, Secretary, Treasurer, 4 Councilors or members-at-large (2 each representing adult and pediatric members), and the chairs of the subcommittees of the organization. There are 5 such subcommittees. A Grants and Manuscript Review Committee undertakes peer review of all grants or manuscripts being submitted under the auspices of the CCCTG. A Guidelines Committee coordinates activities in the area of guideline development and knowledge translation. A Website Committee maintains the CCCTG website (www.ccctg.ca), while an Ethics Committee coordinates activities addressing ethical issues in critical care research. Finally, an Education Committee runs educational activities for trainees. In addition, a member of the Clinical Research Coordinators Group - initiated to address the educational needs and professional development of critical care research coordinators – and a member of the Canadian Critical Care Translational Biology Group (CCCTBG) – founded to promote collaborative basic science research using CCCTG programs as platforms (*vide infra*) – also sit on the Executive Committee.

Scientific meetings of the CCCTG are held three times a year. Two of these meetings take place in locales remote from cities to promote camaraderie and collegiality, and are held over 2 to 3 days with time set aside for leisure activities; the third meeting, held in the fall in association with the Critical Care Canada Forum in Toronto, is an intensive day-long meeting. Members wishing to propose a new research program are required to submit an abstract and draft protocol in advance of the meeting. The proposal is then presented at a meeting for discussion and critique, and a poll taken to assess the level of interest of the membership in hearing further about the project, and in becoming active participants of the research team. The process is quite informal. We have not found a need

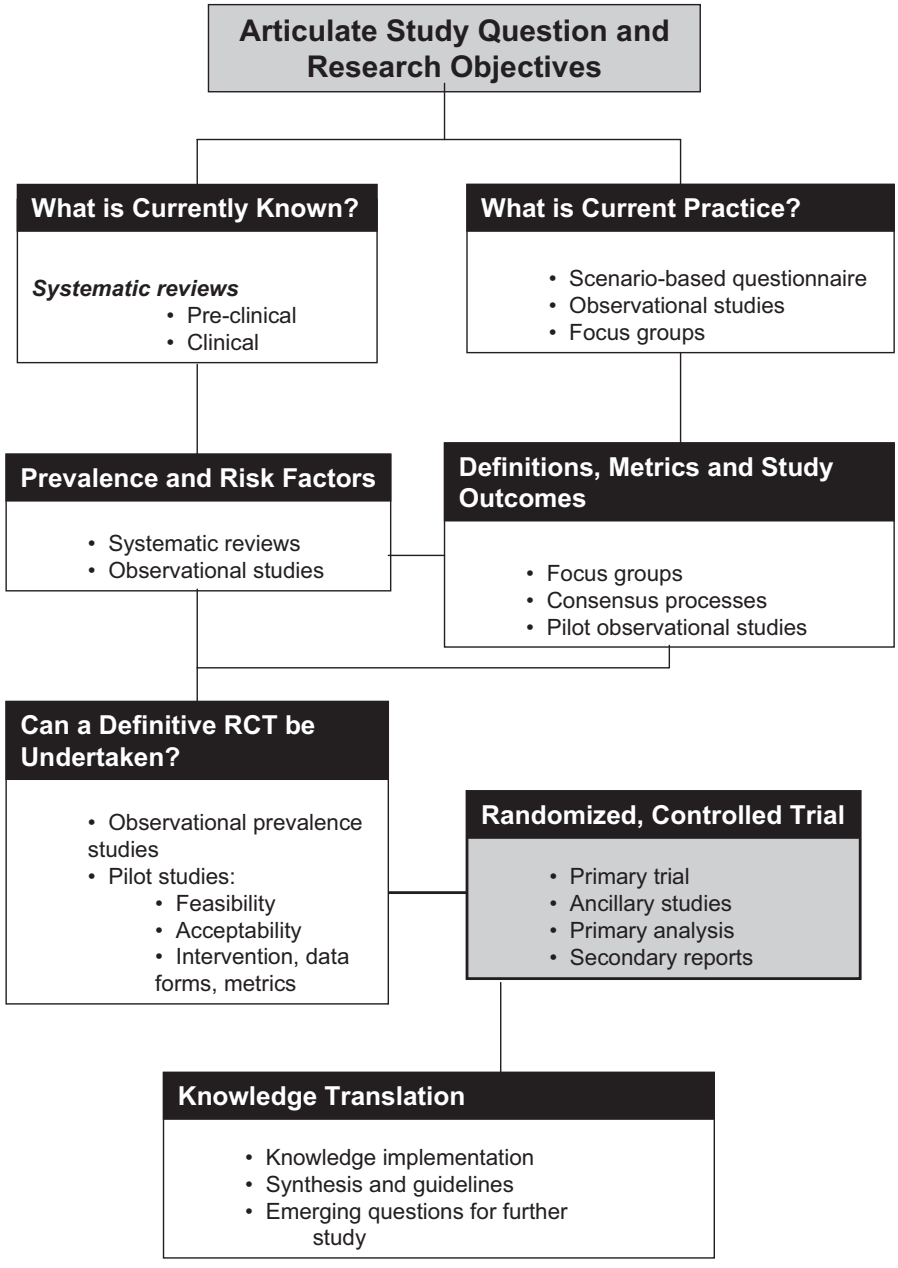

Figure 2. Programmatic research: The Canadian Critical Care Trials Group model of clinical research entails the answering of a question. While an adequately powered randomized controlled trial (*RCT*) is a component of this process, the Canadian Critical Care Trials Group has evolved the philosophy that the process involves multiple steps to systematically evaluate what is known, to characterize clinician behavior, to determine whether the question can be addressed, and ultimately, to translate the results of clinical research so that clinical practice is changed. These elements comprise a programmatic model of clinical research.

to reject potential projects that have achieved a sufficient level of development to be presented to the group, but rather have observed that those that fail to evolve disappear by attrition, an occurrence which is relatively uncommon.

The principal investigator of any CCCTG-affiliated research program is expected to provide updates on the progress of the research at each meeting, even if only in an abbreviated form, and to lead more intensive discussions with the membership on a regular basis. These protocol discussions are both the scientific highlight of our meetings, and for the investigator, the most valuable aspect of CCCTG membership. After providing a brief summary of the project and its progress since the last meeting, the investigator poses specific questions for discussion. The scope of these questions is broad, and may include nuances of the study question, inclusion and exclusion criteria, outcome measures, funding, strategies to increase recruitment, or future research directions. Minutes are taken at these discussions and the investigator is provided with a summary of the key points that emerge.

Trials and Tribulations

Since its inception almost two decades ago, the CCCTG has published more than 60 peer-reviewed papers, including nine in the *New England Journal of Medicine*. In addition, we have published a large number of abstracts, as well as peer-reviewed manuscripts relating to CCCTG programs, although not formally authored by the group. We have enjoyed considerable success with peer review funding agencies, having been successful with 8 of the last 11 grant applications submitted to the Canadian Institutes for Health Research. Our current research portfolio includes more than 30 programs, led by more than two dozen different investigators; some of these are summarized in Table 1.

A recent survey of member sites provided insight into current resources, and the immediate challenges faced by the CCCTG. We surveyed 26 centers recruiting patients to CCCTG trials (20 adult and 6 pediatric ICUs). These ICUs staffed 609 critical care beds (median 22), and admitted 2698 patients (median 92; range 45 to 250) during the study month of April 2005. They recruited patients to an average of 1.7 (range 0–4) industry-sponsored trials, 1.4 (range 0–5) CCCTG trials, and 1.7 (range 0–7), investigator-initiated, non-CCCTG trials. Sites recruited an average of five critically ill patients to a research study each month, although there was considerable variability in recruitment success among units (Fig. 3). We have set an objective of recruiting 12% of patients admitted to a research endeavor. Only four centers (15%) achieved this target during the study month; it is clear that there is an unmet opportunity for greater productivity in CCCTG centers.

Of the 26 responding centers, 21 (81%) indicated that they employed a research coordinator for ICU-based clinical research. Sources of salary support for this individual varied. Industry-funded clinical trials were the most important source of salary support: 76% of ICUs employing a research coordinator de-

Table 1. The Canadian Critical Care Trials Group research portfolio

Study	Lead Investigator	Research Focus	Status
Appropriate Antimicrobial Therapy in Critical Care	Mary-Anne Aarts, John Marshall	Empiric antibiotic therapy for suspected ICU-acquired infection	Survey, observational study, and meta-analysis published; pilot RCT complete and under review
ABATE Ventilator-Associated Pneumonia	John Muscedere, Tasnim Sinuff	Knowledge translation of guidelines for the prevention of ventilator-associated pneumonia	Knowledge translation study funded and in progress
ABLE: Age of Blood Evaluation	Paul Hébert, Jacques Lacroix	Age of transfused red blood cells	Systematic review and pilot RCT completed Definitive 2510 patient trial funded
Adrenal Insufficiency in the Pediatric ICU (PICU)	Kusum Menon	Prevalence of adrenal insufficiency and use of steroids in PICU	Data collection ongoing
A Fib	Sal Kanji	Management of new-onset atrial fibrillation	Systematic review complete; pilot study recruiting
CONSENT	Karen Burns	Barriers to informed consent for ICU research	Observational study funded and to be initiated
Early Determination of Neurologic Prognosis in Brain Injury	Alexis Turgeon	Predictors of outcome in TBI	Systematic review completed; observational studies and survey in progress
Fluids after Cardiac Surgery	Sheldon Magder	Colloids vs. crystalloids after cardiac surgery	Pilot study completed
Hyp-HIT	Jamie Hutchison	Hypothermia for pediatric head injury	240-patient clinical trial complete; manuscript published, NEJM
OSCILLATE	Niall Ferguson, Maureen Meade	High frequency oscillation for acute lung injury	Systematic review complete; pilot study complete
PRECISE	Lauralyn McIntyre	Crystalloids vs colloids in septic shock	Pilot study completed; practice surveys completed; RCT proposal submitted for funding
PROTECT	Deborah Cook	Prophylaxis of venous thromboembolism	Multiple observational studies complete Evaluation of bioaccumulation of low molecular weight heparin, accepted for publication Pilot studies of protocol published 3600-patient RCT recruiting
REDOXs	Daren Heyland	Anti-oxidant-enhanced enteral nutrition	Pilot study completed; 1200 patient RCT funded and recruiting
Toward RECOVER	Margaret Herridge	Quality of life, caregiver burden, and neuromuscular sequelae in ICU survivors	Pilot studies ongoing
Resident Work Hours Study	Chris Parshuram	Models of on-call during critical care training	Three surveys completed Survey completed Trial funded and recruiting
SLEAP	Sangeeta Mehta	Sedation	Pilot RCT completed; 425-patient RCT funded and recruiting
SUGAR: Survival Using Glucose Algorithm	Dean Chittock	Tight glucose control	Collaboration with Australia and New Zealand Intensive Care Society Clinical Trials Group NICE trial; 6100-patient study completed
Validation of Severity of Illness Scoring Systems in PICUs	David Wensley	Validation of PRISM and PIM-2	Data from more than 8000 admissions collected
Vasopressin in Pediatric Shock	Karen Choong	Vasopressin in septic children	69-patient pilot study completed
WEAN: Wean Early and Automatically using New Algorithm	Karen Burns, François Lellouche	Automated weaning protocol	Pilot study recruiting

ICU, intensive care unit; RCT, randomized controlled trial; TBI, traumatic brain injury; NEJM, *New England Journal of Medicine*; PRISM, Pediatric Risk of Mortality; PIM, Pediatric Index of Mortality.

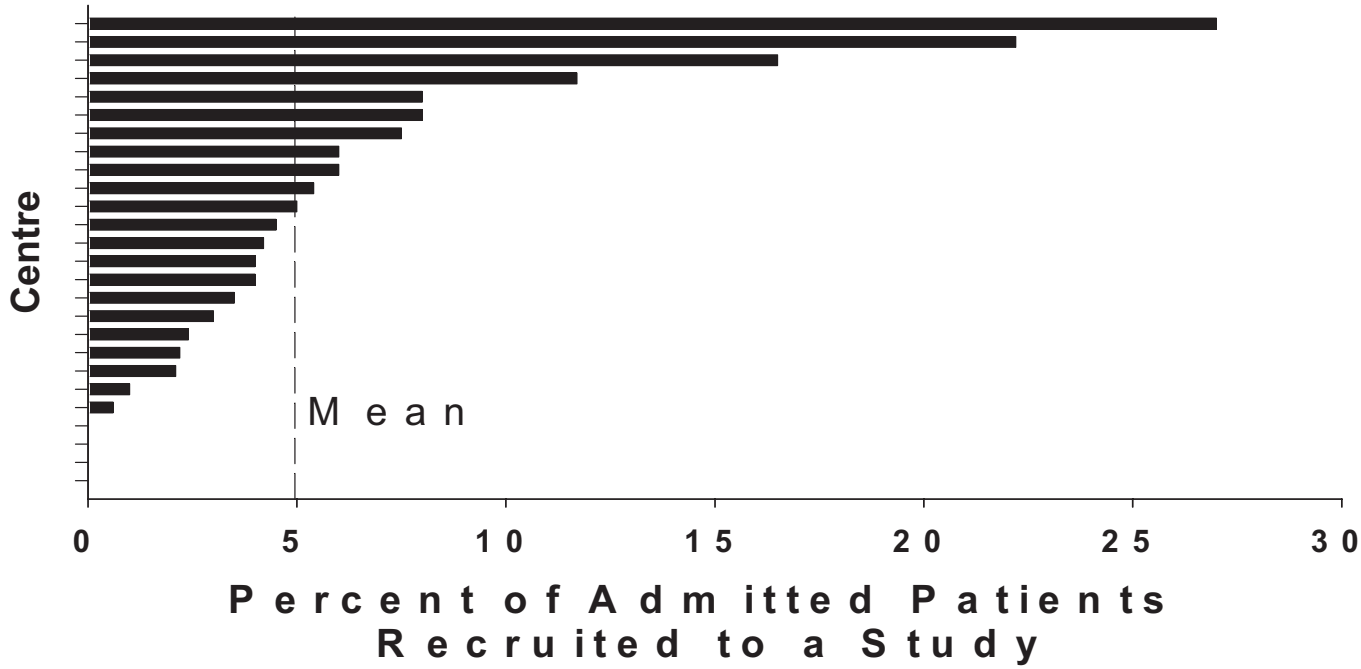

Figure 3. Recruitment rates to clinical studies in Canadian Critical Care Trials Group-participating centers. Across the 25 centers evaluated, the mean number of patients recruited to a clinical study during the month of April 2005 was 5.

pended on this source of salary funding, either in whole or in part. Other sources of coordinator salary support included per-patient payments from peer review-funded CCCTG trials, institutional support, other academic funds, and clinical earnings of the ICU staff. Sustainable and secure funding for research coordinator salary was identified as the single greatest need, and the greatest threat to ongoing participation in clinical research. In Canada, salary funding from peer review granting agencies for funded clinical trials is modest, and per-patient reimbursement for CCCTG studies is typically in the range of $1000 to $1500 CAN$ per patient. In the face of rising pharmacy and other study costs, reimbursement from CCCTG trials is insufficient to meet salary expenses. Industry-funded studies typically provide generous reimbursement schemes, enabling sites to use overage generated from these studies to close the salary gap. However industry-funded studies are an inconsistent source of funding, compete for eligible patients, and consume considerable amounts of coordinator time. Thus finding alternate means of providing secure funding over time for research coordinators has emerged as the primary need of the CCCTG, and the primary threat to our future success.

Half of our recruiting sites indicated that they sometimes recruited patients to more than one clinical trial. The ethical and statistical issues associated with co-enrollment of patients in more than one clinical trial are complex. They are also the focus of a current research initiative undertaken by the CCCTG in collaboration with members of the Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG). On the one hand, co-enrollment improves research efficiency and expedites the answering of questions that can ultimately improve patient care. On the other hand, co-enrollment may pose an extra burden on family members who are approached for third party consent, and if there is a potential interaction between interventions, may alter anticipated rates of the expected outcome (although randomization should minimize systematic bias resulting from one or other intervention).

Other themes emerged as future needs for the CCCTG, and these are shaping our efforts to secure infrastructural support. Methodologic support for CCCTG studies has been typically provided by the home institution of the principal investigator. While a number of our centers house well-developed, cutting edge clinical research units, it is apparent that research in the critically ill poses unique methodologic challenges, and benefits from the availability of dedicated methodologists to optimize research conduct. Thus we are seeking support to develop a decentralized network of methods centers and to establish common research data platforms and monitoring methods for future CCCTG-funded trials.

Yet another area of challenge identified by our needs assessment survey arises through interactions with institutional research ethics boards (REBs). Interventions in the intensive care unit are typically urgent, and decisions must be made without delay; study of the management of these urgent clinical problems requires that consent be obtained rapidly, and patients be randomized expeditiously. Yet by virtue of the problem that has brought the patient to the ICU, critically ill patients are rarely able to provide informed first person consent to participate in clinical trials, and consent must be obtained from a substitute decision-maker. In upholding a mandate to protect vulnerable research subjects, Research ethics boards often place restrictions on the obtaining of consent for ICU research. Even in the absence of approval of alternate models of consent such as deferred consent, REB policies often prohibit telephone consent or faxed consent forms, with the result that potentially eligible study subjects are excluded from participation. Thus another area of current research interest within the CCCTG is the process of informed consent for critical care research – another theme

that has opened further collaborative opportunities with the ANZICS CTG.

Clinical Research as a Platform for Additional Research

The process of research in ICUs generates multiple questions that are appropriate and important themes for research, and investigator-led research consortia are ideally positioned to address these. The CCCTG has used its research programs as platforms for a number of such ancillary studies; in a number of cases, the initiative was led by a research coordinator.

For example, we analyzed data from a screening log maintained to monitor recruitment into multiple trials in order to develop metrics to understand variability in recruitment rates, and to devise strategies to maximize enrollment into future studies (25). Another coordinator-initiated study evaluated the time spent by a research coordinator in tasks other than data collection during the initiation and maintenance of a clinical trial (2, 26). More recently we have initiated research programs addressing informed consent in the critically ill, and the need for improved outcome measures for use in clinical trials.

Approximately 7 years ago, a group of CCCTG members with active basic science research interests established the Canadian Critical Care Translational Biology Group to promote collaborative basic and translational research in association with the CCCTG, and to take advantage of opportunities such as clinical data collection or the use of a systematic study intervention to study the biology of critical illness. They have published their first manuscript (27) and are initiating further collaborative studies.

International Collaboration: Opportunities and Needs

The CCCTG has served as a model for other collaborative, investigator-led clinical research groups. With their rapidly evolving success, the potential for international collaborative research has become a reality. We have, for example, conducted a number of studies in collaboration with the ANZICS CTG, and with investigators in the United States, England, France, Sweden and Saudi Arabia. This collaborative spirit, for example, has generated the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation study, initiated by the ANZICS CTG, and separately funded by the Canadian Institutes for Health Research which is evaluating the benefits of tight glucose control in an heterogeneous population of critically ill patients. Enrollment concluded in August 2008, after more than 6100 patients had been randomized, making the trial one of the largest ICU studies ever conducted, and holding the promise of providing a definitive answer to an important area of contemporary controversy.

Preliminary discussions have been held with investigator-led clinical research groups in North America, South America, Europe, Africa, and Australasia, under the auspices of the World Federation of Societies of Intensive and Critical Care Medicine, with the goal of holding regular discussions on themes of common interest, and ultimately, of promoting global, investigator-led collaborative critical care research.

Conclusions: The CCCTG and the Future of Investigator-Led Clinical Research In Critical Illness

Two decades after our first meeting, the CCCTG finds itself embracing successes that far exceed our fondest early hopes. Canadian investigators lead the world in productivity in critical care research, whether measured as a function of population or gross domestic product (28), and the CCCTG has played an important role in establishing this preeminence. The commitment of a talented group of experts has been a fundamental element of our success. However three additional factors have been of immense importance.

First, we have chosen to study questions that reflect the daily concerns of practicing intensivists. This has responded to a previously unmet need in a field in which clinical research initiatives were dominated by commercial studies undertaken for product registration, or studies that reflected an individual investigator's desire to better understand the clinical state of critical illness. This focus has struck a responsive chord with granting agencies, journals, and a new generation of clinician investigators who present new ideas at our scientific meetings.

Second, we have created a collaborative structure that combines scientific rigor with intense collegiality. Our increasingly mature processes of research oversight and mentoring ensure that CCCTG protocols are well thought out, and scientifically rigorous. These formal processes also provide our membership with an ongoing process of informal mentoring and education through lively discussions at our scientific meetings. We hold regular educational sessions for research coordinators, and recently have initiated a program for critical care trainees, with the objective of educating the next generation of Canadian critical care researchers.

Finally, we have successfully nurtured a culture of genuine respect and collegiality. This culture has been facilitated by holding our meetings in out-of-town recreational sites, rather than in airport hotels or convention centers, by building recreational time into the scientific agenda, and by ensuring ample time in the evening for good food and wine, to accompany impassioned conversation.

The remarkable success of the CCCTG argues persuasively for new models of critical care research. Just as investigator-led research has become the norm in oncology and cardiology, so we believe that a shift from commercial to investigator-led clinical research holds the greatest promise for systematic study of the risks and benefits of what we do, and even for high-quality study of novel diagnostic and therapeutic strategies. The possibilities are truly extraordinary.

REFERENCES

1. Keating P, Cambrosio A: From screening to clinical research: The cure of leukemia and the early development of the cooperative oncology groups, 1955–1966. *Bull Hist Med* 2002; 76:299–334
2. Cook D, Rocker G, Marshall J, et al: Levels of care in the intensive care unit: A research program. *Am J Crit Care* 2006; 15:269–279
3. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
4. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
5. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
6. Freedman B: Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317: 141–145
7. Fisher B, Bauer M, Margolese R, et al: Five year results of a randomized clinical trial comparing total mastectomy and segmental

mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985; 312:665–673
8. Brower RG, Matthay MA, Morris A, et al: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301–1308
9. National Heart LaBIARDSACTN, Wiedemann HP, Wheeler AP, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
10. Cook DJ, Guyatt GH, Marshall JC, et al: A randomized trial of sucralfate versus ranitidine for stress ulcer prophylaxis in critically ill patients. *N Engl J Med* 1998; 338:791–797
11. Cook DJ, Laine LA, Guyatt GH, Raffin TA: Nosocomial pneumonia and the role of gastric pH: A meta-analysis. *Chest* 1991; 100: 7–13
12. Cook DJ, Witt LG, Cook RJ, et al: Stress ulcer prophylaxis in the critically ill: a meta-analysis. *Am J Med* 1991; 91:519–527
13. Cook DJ, Fuller H, Guyatt GH, et al: Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330: 377–381
14. Cook D, Heyland D, Griffith L, et al: Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med* 1999; 27:2812–2817
15. Cook DJ, Griffith LE, Walter SD, et al: The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001; 5(6):368–375
16. Heyland DK, Cook DJ, Griffith L, et al: The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. *Am J Respir Crit Care Med* 1999; 159:1249–1256
17. Heyland DK, Cook DJ, Marshall JC, et al: The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. *Chest* 1999; 115:1076–1084
18. Canadian Critical Care Trials Group, Heyland D, Dodek P, et al: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006; 355: 2619–2630
19. Hebert PC, Wells G, Blajchman MA, et al: A multicentre randomized controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409–417
20. Hebert PC, Wells G, Martin C, et al: A Canadian survey of transfusion practices in critically ill patients. *Crit Care Med* 1998; 26: 482–487
21. Hebert PC, Wells G, Martin C, et al: Variation in red cell transfusion practice in the intensive care unit: a multicentre cohort study. *Crit Care* 1999; 3:57–63
22. Hebert PC, Wells G, Marshall J, et al: Transfusion requirements in critical care. A pilot study. *JAMA* 1995; 273:1439–1444
23. Cook D, Heyland D, Marshall J, et al: On the need for observational studies to design and interpret randomized trials in ICU patients: A case study in stress ulcer prophylaxis. *Intensive Care Med* 2001; 27:347–354
24. Aarts MA, Granton J, Cook DJ, et al: Empiric Antimicrobial Therapy in Critical Illness: Results of a Surgical Infection Society Survey. *Surg Infect* 2007; 8:329–336
25. Foster D, Cook D, Granton J, et al: Use of a screen log to audit patient recruitment into multiple randomized trials in the intensive care unit. *Crit Care Med* 2000; 28:867–871
26. McDonald E, Clarke F, Dale C, et al: ICU research coordinator activities: A multicenter time in-motion study. *J Crit Care* 2005; 9:P267
27. Haqqani AS, Hutchison JS, Ward R, et al: Biomarkers and Diagnosis; Protein Biomarkers in Serum of Pediatric Patients with Severe Traumatic Brain Injury Identified by ICAT-LC-MS/MS. *J Neurotrauma* 2007; 24(1):54–74
28. Michalopoulos A, Bliziotis IA, Rizos M, et al: Worldwide research productivity in critical care medicine. *Crit Care* 2005; 9:R258–R265