Advancing intensive care research in Australia and New Zealand: development of the binational ANZIC Research Centre

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ABSTRACT

Over the past 12 years, the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group and the broader intensive care community in Australia and New Zealand have established a track record for conducting high quality, investigator-initiated clinical research in critically ill patients. This is highlighted by the publication of the SAFE (Saline Albumin Fluid Evaluation) study in the *New England Journal of Medicine* and the MERIT (Medical Early Response Intervention and Therapy) study in the *Lancet*.

Here, we discuss potential impediments to the further advancement of intensive care research in Australia and New Zealand, and suggest strategies to address them. We propose that there is a need to broaden the current research scope and develop more multifaceted research programs that address clinically important issues. We stress the need to also undertake phase II studies to assess safety, pharmacokinetics and biological plausibility of new and established therapies. In addition, we highlight limitations imposed by the relatively small regional population of Australia and New Zealand, and the need to develop international collaborations to allow trials requiring large sample sizes.

We contend that the best chance of improving outcomes in many disease states requires studies to commence before patients enter the ICU, which will depend on collaboration with established and emerging craft groups, such as ambulance services, emergency medicine and anaesthesia. We also emphasise the need to study system factors affecting patient outcomes, as well as the translation of research findings into clinical practice. Finally, we describe the establishment and objectives of the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) and outline the Centreís current projects in the context of an integrated research framework.

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The hospital mortality of patients admitted to intensive care in Australia and New Zealand is about 15%.[1] Intensive care is expensive, consuming an estimated A$500 million to $1 billion in Australia per annum.[2] There is an imperative to improve patient outcomes and reduce associated costs of intensive care medicine in our countries.

In recent years, Australian and New Zealand intensivists have established an international reputation for conducting high quality, investigator-initiated clinical research in critically ill patients.[3] This track record has been achieved both by individuals and by highly productive collaborative activities within the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG).[1] Established in 1994, the ANZICS-CTG has published a number of high-impact studies of increasing complexity and size, including a trial of low-dose dopamine for patients with early acute renal failure (*n*=328, *Lancet* 2000),[4] the Saline Albumin Fluid Evaluation (SAFE) study (*n*=6997, *New England Journal of Medicine* 2004),[5] and the Medical Early Response Intervention and Therapy (MERIT) study (a cluster randomised trial in 23 hospitals, Lancet 2005).[6]

Impediments to advancing ICU research in Australia and New Zealand

The conduct of future phase III randomised trials in critically ill patients in Australia and New Zealand is limited by a number of factors, including barriers to patient recruitment, obtaining funding in a timely manner, and consent issues specific to the critically ill. An additional consideration, particularly in drug trials, is the altered pharmacokinetics associated with critical illness. While some of these factors are universal to clinical research, others are specific to the ICU patient population.

Study recruitment rates and need for international collaborations

Patients in the ICU are heterogeneous, in terms of both their disease process and the therapies they undergo. The ability to demonstrate effectiveness of a novel therapy is therefore restricted and potentially confounded by many variables. Although large multicentre studies can overcome these problems, recruitment rates are limited by the modest size of our regional populations and the increasing demands of competing studies.

Table 1. Summary of projects initiated during the inaugural year (2006) of the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)

Study title	Chief investigator	Description of study	Funding source	Collaboration with the ANZIC-RC
ATBIS (Australasian Traumatic Brain Injury Study)	John Myburgh	3-month inception cohort study of traumatic brain injury in Australia and New Zealand	Victorian Trauma Foundation	ANZICS-CTG
STATInS (Study of Atorvastatin Therapy In Sepsis)	Peter Kruger	Phase II randomised controlled trial of atorvastatin in severe sepsis	NHMRC 2007	ANZICS-CTG University of Queensland Princess Alexandra Hospital
ARISE study (Australasian Resuscitation In Sepsis Evaluation)	Sandra Peake	Observational study of patients presenting to the emergency department with septic syndromes	Intensive Care Foundation	ANZICS-CTG Queen Elizabeth Hospital Adelaide Australasian College for Emergency Medicine
Heparin in Severe Sepsis	Megan Robertson	Pilot study of low dose heparin in sepsis	Intensive Care Foundation	ANZICS-CTG Royal Melbourne Hospital
SAFE-TRIPS (Saline Albumin Fluid Evaluation Translation of Research Into Practice Study)	Simon Finfer	Study of administration of fluid for resuscitation in patients admitted to ICU	Unfunded	George Institute for International Health Multiple collaborators worldwide
CAT (CATecholamine) study	John Myburgh	Phase II randomised controlled trial of adrenaline versus noradrenaline for ICU patients with shock	ANZCA 2005	Royal Brisbane and Women's Hospital Royal North Shore Hospital St Vincent's Hospital Melbourne St George Hospital
PASS study (Pituitary–Adrenal axis in Septic Shock)	Bala Venkatesh	Assessment of the role of relative adrenal insufficiency in patients with septic shock	Unfunded	ANZICS-CTG Princess Alexandra Hospital University of Queensland
IVIG in Sepsis (Intravenous Immunoglobulin in Sepsis)	Rinaldo Bellomo	Phase II study of effect of intravenous immunoglobulin on outcomes from severe sepsis	Unfunded	ANZICS-CTG Initiated from ANZIC-RC Collaboration with ARCBS
BioMARK (Biological Markers of Recovery in the Kidney)	Carlos Scheinkestel	Study of the role of inflammatory cytokines and oxidative stress in acute renal failure	Unfunded	ANZICS-CTG RENAL study investigators

ANZICS-CTG = Australian and New Zealand Intensive Care Society Clinical Trials Group. NHMRC = National Health and Medical Research Council. ANZCA = Australian and New Zealand College of Anaesthetists. ARCBS = Australian Red Cross Blood Service. ◆

As an example, the SAFE study enrolled 6997 patients. The trial was designed to provide a power of 90% to detect a 3% difference in absolute mortality rates between the two groups, from an estimated baseline mortality rate of 15%.[5] A trial of this size was possible because the patients enrolled had broad inclusion and narrow exclusion criteria, the intervention studied was commonly used and easy to implement, and a deferred consent strategy was both ethical and feasible. Recruitment of a similarly sized but more highly selected cohort of ICU patients (eg, severe sepsis or traumatic brain injury) may not be feasible in an achievable time frame in Australia and New Zealand, because of regional population constraints. In addition, enrolment of a specific patient cohort into multiple different and competing trials further reduces the recruitment rate for any individual trial.

An important strategy to overcome these limitations is to join with international collaborators to ensure adequate sample sizes and appropriate generalisability for many of our key research questions. Recent examples of successful collaborations between Australian, New Zealand and Canadian investigators in randomised controlled trials include the VASST (low dose vasopressin in septic shock), DECRA (decompressive craniectomy in traumatic brain injury), NICE-SUGAR (glucose control regimens in ICU), and PROTECT (unfractionated versus low molecular weight heparin for venous thromboembolism prophylaxis) studies.

Obtaining commensurate funding in a timely manner

Conducting clinical research in critically ill patients is expensive. The major regional research funding body in Australia is the National Health and Medical Research Council

(NHMRC). Currently, the NHMRC reviews grant submissions once per year, creating considerable time pressures in the research planning process. The limited number of additional funding sources and the relative infrequency of grant rounds have resulted in lost opportunities to perform add-on studies to our large randomised controlled trials, such as NICE (Normoglycaemia in Intensive Care Evaluation), SAFE and RENAL (Randomised Evaluation of Normal versus Augmented Level of renal replacement therapy in ICU).

Since 2001, 28 studies endorsed by the ANZICS-CTG have attracted more than A$18 million. Although the amount of funding per study is progressively increasing, it remains substantially less than funding for similar studies internationally. For example, the NHMRC-funded NICE study is able to reimburse sites at A$235 per patient. The Canadian Institute of Health Research-funded (and equivalent) SUGAR (Survival Using Glucose Algorithm Regulation) study is currently reimbursing at Can$1000 per patient. A major challenge for the chief investigators of future grant submissions is to be proactive in obtaining reimbursement that is commensurate to the time commitment and level of expertise[7,8] of our research coordinators.

Issues of consent and enrolment in the critically ill

The average ICU length of stay is 3 days, and for most studies of ICU therapy there is a limited window of opportunity to obtain consent and enrol eligible patients. The critically ill are vulnerable and dependent on the ICU team for their care and therapy.[9] In addition, they are frequently unable to give informed consent, and most often this must be obtained from a next of kin or alternative legal surrogate.[9] Recruitment into large randomised trials may be enhanced if delayed consent is allowed, such as has been the case in the SAFE and RENAL studies.

Early phase studies within multifaceted research programs

To date, the phase III trials undertaken by the ANZICS-CTG have tested the effectiveness of commonly prescribed, but unproven, therapies. The low-dose dopamine trial compared the effects of low-dose dopamine to placebo in the treatment of early acute renal failure.[4] Similarly, the SAFE trial assessed the effectiveness of saline and albumin as resuscitation fluids in the critically ill.[5]

Just as large phase III effectiveness trials will remain important to inform clinical practice, phase II safety and efficacy trials are likely to become a more common feature of ICU research that will inform the design of phase III trials. Patients in the ICU may have impaired hepatic and renal function that reduces drug clearance in an unpredictable manner. In addition, ICU patients may develop variable degrees of capillary leak, tissue oedema and hypoalbuminaemia, all of which affect the volume of distribution of a drug.[10] Phase II trials offer a means to assess pharmacokinetics, establish optimum dosage schedules and assess drug safety;[11] at the same time, they provide important information on potential recruitment rates and treatment effects that underpin the feasibility of larger trials. As an example, the recent DIRECT (Dalteparin's Influence on Renally Compromised: anti-Ten-A) trial assessed the effects of critical illness and renal failure on the pharmacokinetics of dalteparin.[12] Further examples of phase II trials in ICU patients include the recently funded ANZICS-CTG-endorsed phase II study of atorvastatin in severe sepsis (see below) and a randomised control trial of adrenaline and noradrenaline in the resolution of acute circulatory failure in critically ill patients (the CAT study) conducted in four Australian ICUs. The latter study provides hitherto unknown information about the feasibility of conducting a large-scale mortality-based study of two established, but under-studied, drugs in critical care medicine.

Expanding the scope of ICU research

Need to extend research to the period before ICU admission

Patients in the ICU may be admitted from several sources, including the emergency department, the operating room and the general ward. In many cases, the pathological process leading to ICU admission has been evolving for some time before critical care physicians and nurses become involved. The Early Goal-Directed Therapy (EGDT) study is an example of a study where initiating treatment of a disease process (sepsis) in the period before ICU admission was associated with improved outcome.[13] In addition, a number of studies have shown that cardiac arrests[14-16] and unplanned ICU admissions[16,17] are associated with abnormalities in vital signs that may be present for up to 24 hours before presentation to the ICU. These observations led to the concept of the medical emergency team (MET)[18] and the conduct of the MERIT study[6] to test the effectiveness of the concept.

Extending our research efforts to the period before ICU admission will require collaboration between emerging and established craft groups, such as the Australian and New Zealand College of Anaesthetists Trials Group, the Emergency Medicine Clinical Trials Group and the Australasian Trauma Society Research Committee.

Importance of system factors to patient outcomes

To date, most ICU research in Australia and New Zealand has focused on the effectiveness or safety of a therapy which is compared with either a placebo or another established therapy. Less information exists on system factors in the ICU

and hospital that influence patient outcomes. For example, a recent single-centre study reported that night-shift discharge from the ICU was associated with increased hospital mortality in ICU survivors.[19] Research into the functioning of health care systems may provide insight into the factors that contribute to unplanned readmission and unexpected deaths after ICU discharge.

Need for cohesive and integrated research programs

Important prerequisites for the design of a phase III randomised trial are:

- demonstration of clinical uncertainty over the effectiveness of interventions being studied;
- knowledge of the current outcome for the condition in question;
- assessment of the potential risk reduction that might reasonably result from the test intervention; and
- an estimation of the number of patients eligible for recruitment in the participating centres.

Inception cohort studies and pilot studies can provide this information and may be an essential prerequisite to successful grant applications and the successful conduct of randomised trials. Often the information needed to derive these variables is not immediately available, and must be prospectively or retrospectively collected.

Increasingly, there is a need to develop multifaceted research programs that assess multiple aspects of a research question. Examples of successful research programs include the VTE (venous thromboembolism) in Medical–Surgical Patients Research Program[11,12] and the McMaster Transfusion Research Program.[20] These and similar programs include literature reviews, meta-analyses, observational and pilot studies, and, finally, randomised, controlled trials. All these facets may be better integrated and achieved by focusing the national effort. For example, a recently published inception cohort study by the ANZICS-CTG assessed the incidence and outcome of severe sepsis in adult ICU patients.[21] This study has allowed estimations of recruitment rates and sample size calculations for a number of planned trials in this patient cohort.

The Australian and New Zealand Intensive Care Research Centre

Establishing the ANZIC-RC

The Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) was established in October 2005 with a 5-year enabling grant from the NHMRC.[22] The grant reflected the track record of the ANZICS-CTG and the founding chief investigators in clinical research, and the need to establish a high-quality clinical research centre which would benefit intensive care in both countries.

The ANZIC-RC is co-funded by Monash University and is located within the Universityís Department of Epidemiology and Preventive Medicine, at the Alfred Medical Research and Education Precinct in inner Melbourne. The core business of the ANZIC-RC is the design and conduct of world-class clinical (phase II and III) trials and epidemiological studies in intensive care medicine. In addition, it will be a binational centre providing intensivists at all levels with training in clinical research. Such a centre has not existed previously in Australia or New Zealand.

Aims of the ANZIC-RC

The ANZIC-RC will be:

- A binational clinical trials methods centre with high level epidemiological, data management and biostatistical consultants, experienced intensive care clinical researchers and the infrastructure to support small, medium and large-scale clinical trials. The centre will establish comprehensive, multifaceted research programs, including surveys, pilot studies and randomised trials. Many of these trials and programs will be linked to the ANZICS-CTG, while some will originate from independent researchers or groups using the research centre facilities or expertise.
- A centre for the further education and training of intensive care clinicians, allied health personal and higher degree students (MD, PhD and MPH) in the design, funding, management and execution of clinical trials.
- A referral centre and source of advice and collaboration for intensivists in Australasia.

Additional goals of the ANZIC-RC will be:

- to initiate and further develop collaborations with other Australian and international research centres, including The George Institute for International Health (University of Sydney) and The Canadian Critical Care Trials Group; and
- to support research trials and programs that broaden the scope of existing ICU research activities to related patient cohorts: pre-hospital, emergency, trauma, perioperative and post-ICU care.

Research activities of the ANZIC-RC in the inaugural year

A number of research projects were commenced in 2006, the inaugural year of the ANZIC-RC. The projects were developed to support the aims of the centre and included both observational studies and randomised controlled trials (Table 1). Four ANZICS-CTG-endorsed NHMRC project grants were submitted, and the ANZICS-CTG-endorsed Australasian Traumatic Brain Injury Study was completed, and the first manuscript was submitted for publication. In addition, three other studies were commenced: the translation of the SAFE study findings into clinical practice; a study

assessing the potential for collaboration with a US National Institutes of Health-funded trial of early goal-directed therapy for septic shock patients (the ARISE study); and a third study investigating the therapeutic potential of heparin in patients with septic shock.

Australasian Traumatic Brain Injury Study (ATBIS)

The ANZICS-CTG-endorsed ATBIS has been completed, and the first manuscript accepted for publication in the *Journal of Trauma*.[23] ATBIS was a prospective 6-month inception cohort study of patients with traumatic brain injury in Australia and New Zealand. The study documented information on the mechanisms of injury, occurrence of secondary brain injuries, management strategies and long-term outcomes at 6 and 12 months. The role of the ANZIC-RC was to analyse the original data set and to prepare and submit two manuscripts: the overall epidemiology, management and outcome of the patient cohort;[23] and a detailed analysis of the ICU management of traumatic brain injury (in preparation).

SAFE-TRIPS: a translation of research into practice study

SAFE-TRIPS is an international collaboration coordinated from The George Institute for International Health and the ANZIC-RC. The aim of SAFE-TRIPS is to determine fluid resuscitation practices around the world following the publication of the SAFE study. The project will be conducted in two phases.

Phase 1 is a description of albumin use in multiple countries worldwide (including Australia and New Zealand) for the period January 1995 to December 2005. This period includes the publication of the Cochrane Review in 1998,[24] and subsequently the main findings of the SAFE study in 2004.[5]

Phase 2 is a point prevalence study to determine fluid resuscitation practices around the world. The study aims to determine whether there are identifiable patient characteristics that influence choice of fluid; whether there are identifiable national or regional variations in choice of resuscitation fluid that are not explained by patient characteristics; and the degree to which evidence from related contemporaneous literature has been translated into practice.

Australasian Resuscitation In Sepsis Evaluation (ARISE)

The ARISE study is a prospective observational study that will assess the characteristics, resuscitation practices, and outcomes of patients presenting to Australian and New Zealand emergency departments with severe sepsis and septic shock. In 2001, a single-centre study in the United States demonstrated that early goal-directed therapy in this patient population was associated with a 16% reduction in absolute risk of death when compared with standard care.[13] The theory underlying this therapeutic approach was that, in patients with severe sepsis, the introduction of a resuscitation algorithm to optimise central venous oxygen saturation shortly after hospital admission would reduce occult organ hypoperfusion, prevent multi-organ dysfunction associated with severe sepsis, and improve outcomes. This study was awarded funding in the 2006 grant round of the Intensive Care Foundation.

Heparin in Severe Sepsis program

The ANZICS-CTG-endorsed Heparin in Severe Sepsis study is a collaboration with investigators at the Royal Melbourne Hospital. A number of recent studies have assessed the interaction of the coagulation and inflammatory cascades in sepsis. In studies of human activated protein C, antithrombin II and recombinant tissue factor pathway inhibitor, administration of low-dose unfractionated heparin (UFH) was associated with a lower mortality rate in the placebo group compared with patients who did not receive low-dose UFH. The addition of UFH did not reduce the mortality in the treatment groups. The Heparin in Severe Sepsis pilot study will determine the feasibility of performing a large multicentre randomised blinded study to determine if low-dose UFH reduces all-cause 90-day mortality in ICU patients with severe sepsis. It will also determine the incidence of complications associated with administration of low-dose UFH in this patient group. The study received funding in the 2006 grant round of the Intensive Care Foundation.

Study of Atorvastatin Therapy In Sepsis (STATInS)

Statins are a class of drug that has been used for many years to reduce mortality from cardiovascular disease. In addition to their action in reducing hepatic synthesis of cholesterol, they also have anti-inflammatory properties that may be of benefit in the treatment of patients with sepsis.[25] A number of observational studies have reported that patients on statin therapy have a reduced risk of developing sepsis,[26,27] and that, in patients who do develop sepsis, the incidence of severe sepsis and death is reduced in those patients who are already treated with statins.[26] In addition, cessation of pre-existing statin therapy in patients who present with sepsis is associated with a worse outcome compared with those who remained on statin therapy.[28] The aims of this ANZICS-CTG-endorsed study are to conduct a phase II randomised trial in adult ICU patients with severe sepsis to assess:

- the effects of atorvastatin on biological markers and clinical outcomes in severe sepsis;
- atorvastatin population pharmacokinetics and safety profile;

- the number of eligible patients, potential recruitment rates and barriers to recruitment in a large-scale trial; and
- the feasibility and cost of a potentially definitive phase III trial.

This project was funded in the 2006 NHMRC grant round for $600000.

An ANZIC-RC initiated study: the role of IVIG in Sepsis

The aim of this study was to conduct a phase II randomised controlled trial of the effect of intravenous immunoglobulin (IVIG) on outcomes of patients with severe sepsis in the ICU. This grant was not funded in the 2006 NHMRC project grant round. Planning for an observational study to assess the antibody response in ICU patients with septic shock is currently underway.

The CAT (CATecholamine) Study

This study was an investigator-initiated double-blind prospective randomised control trial of adrenaline and noradrenaline in the resolution of acute circulatory failure in a heterogeneous population of critically ill patients. The study was developed with input from the ANZICS-CTG community and received funding from the Australian and New Zealand College of Anaesthetists. The ANZIC-RC conducted the statistical analysis of this study, which is currently under review for publication.

Conclusions

Major achievements in ICU research in Australia and New Zealand have been achieved in the past by committed individual researchers, and more recently by the collaborative efforts of many intensivists working within the ANZICS-CTG. Impediments to the further advancement of ICU research in our region include the limited population, insufficient funding for landmark studies, competing studies in the ICU, and the need for large cohorts of homogeneous patients to obtain clinically relevant answers. Pre-ICU research will be important for many new questions. Hospital- and ICU-related system factors that affect the outcome of ICU patients before and after ICU admission should be defined and investigated. Finally, research hypotheses should be formulated and developed into multifaceted research plans that address multiple aspects of the research question, thereby providing the building blocks for new grant applications and eventual randomised trials. The newly established ANZIC-RC will develop, encourage and conduct research within this framework. It will provide new opportunities previously unavailable to intensivists in our region, and will further enhance the reputation of our specialty.

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