Australian Clinical Trials Alliance



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Senate Select Committee on Health
PO Box 6100
Parliament House
Canberra ACT 2600

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Dear Committee Secretariat,

**RE: Select Committee on Health**

The Australian Clinical Trials Alliance (ACTA) welcomes the opportunity to contribute to the Committee's inquiry into health policy, administration and expenditure in Australia.

**Our submission relates to point e:** ***improvements in the provision of health services, including Indigenous health and rural health.***

We thank the committee for their consideration of these important national issues and would be pleased to provide further information to assist the Inquiry on behalf of Australia's investigator-initiated clinical trials and registries sector.

Prof John Zalcberg OAM

Chair, Australian Clinical Trials Alliance

# Contents

## The Australian Clinical Trials Alliance

The Australian Clinical Trials Alliance (ACTA) was established in 2013 as a national peak body to support high-quality investigator-initiated clinical trials and clinical quality registries within the Australian healthcare system.

The mission of ACTA is to promote effective and cost-effective health care in Australia through investigator-initiated clinical trials that generate evidence to support decision-making by health practitioners, policymakers and consumers (see attached document for further background about ACTA).

The ACTA community encompasses 60 clinical trials networks, clinical trial coordinating centres and clinical quality registries (see Appendix A). Each of these networks comprise up to several hundred senior doctors, nurses, allied health professionals and career researchers, and cover a broad range of disease groups and clinical disciplines.

These groups are among Australia's most productive and high-impact researchers - responsible for establishing the effectiveness, and in some cases the harm, associated with new and/or commonly used investigations and treatment. Trials conducted by these networks have saved or improved many tens of thousands of lives both here and around the world (see Appendix B for examples of high-impact clinical trials conducted by Australian networks).

## The fiscal challenge for twenty-first century healthcare

Since the latter years of the past century, the breadth and complexity of treatment options to optimise the health of individuals has increased exponentially. As a result, health costs are rising rapidly as clinical systems expand to meet these increasing demands.

As this committee will be well aware, the overall level of Australian and state government healthcare expenditure, as well as private healthcare contributions, was estimated to be of the order of $140 billion in 2011-12. These costs are predicted to almost double in the next decade[1].

This relates, in part, to an ageing community, as well as overall growth in population. In addition, this increase is due to a shift in the number of people previously experiencing acute conditions – such as cardiovascular and infectious diseases – which are changing in severity and incidence to chronic states of ill-health due to cancer, obesity and diabetes, dementia and other neurodegenerative conditions, and physical disability related to older age.

The United States (US) Congressional Budget Office predicted that the major driver of increasing costs and the greatest threat to the sustainability of the US healthcare system would be the introduction of new technologies[2].

In this context, it is critical that the real value of new therapeutic approaches can be compared to existing modalities in a manner that addresses their clinical value (i.e. how should the new technology be best used in a cost-effective manner to improve outcomes) rather than their commercial value alone (i.e. how does the new technology compare to the old technology).

[1] AIHW (2014). Health expenditure Australia 2011-12: analysis by sector. Health and welfare expenditure series. Canberra

[2] Congress of the United States Congressional Budget Office (2013). The 2013 Long-term Budget Outlook, http://www.cbo.gov/sites/default/files/cbofiles/attachments/44521-LTBO2013_0.pdf (accessed September 2014)

## The quality challenge for twenty-first century healthcare

High-quality healthcare has been defined in simple terms as getting the right care to the right patient at the right time – every time[3]. By world standards, Australia has a high standard of healthcare, but the degree to which treatments received by Australians are based on best evidence, and are delivered appropriately and consistently across different healthcare services is largely unknown.

ACTA strongly endorsed the findings of the recent report by the Australian Commission on Safety and Quality in Health Care*, Exploring Healthcare Variation in Australia: Analyses Resulting from an OECD Study* which indicated that variation in healthcare interventions and outcomes - and identifying and reducing unwarranted variation - is a critical issue for Australia and our health system.

It is widely accepted that:

- many treatments that are proven to be effective are not provided to patients (failure of translation of evidence into practice);
- many treatments are adopted without proof of effectiveness or knowledge of cost-effectiveness (translation without evidence);
- many variations of standard treatments are widely practiced without knowledge of relative effectiveness and cost-effectiveness (comparative effectiveness); and
- even when treatment is 'best practice based' variation can still occur as a result of other factors such as resource availability, access to care, clinician experience and volume, team morale and clinical leadership.

## Reducing waste, improving efficiency & increasing productivity in healthcare

- Each year in Australia there are over 9 million hospital separations (increasing by around 6% per year), 2.4 million surgical procedures, and more than 200 million prescriptions are issued[4].
- Despite enormous activity within the healthcare sector, comparatively little effort is spent learning about its effectiveness and cost-effectiveness, or systematically monitoring the outcomes achieved for patients.
- It has been variously estimated that fewer than 25% of medical interventions are currently based on high-quality evidence[5] and that as much as 30-50% of healthcare expenditure is wasted[6] .
- Only a tiny fraction of patients that currently receive treatment in Australia have their data collected within a quality registry or are enrolled into a clinical trial.

It is inevitable that all funders of healthcare, as well as the general community, will ultimately demand that escalating costs only be supported if treatments and interventions are based on proof of their effectiveness. That is, evidence that the procedure, drug, device or treatment has been proven to improve patient outcomes – as well as their relative value compared to other treatment options.

[3] US Dept of Health and Human Services, Agency for Health care Research and Quality (2009). What is health care quality and who decides? http://www.hhs.gov/asl/testify/2009/03/t20090318b.html (accessed September 2014)
[4] Australian Institute of Health and Welfare 2013. Australian hospital statistics 2011–12. Health services series no. 50. Cat. no. HSE 134. Canberra: AIHW.
[5] For example, BMJ Clinical Evidence (2014). What conclusions has Clinical Evidence drawn about what works, what doesn't based on randomised controlled trial evidence? http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html (accessed September 2014)
[6] Berwick DM and Hackbarth. Eliminating Waste in US Health Care. Journal of the American Medical Association. 2012; 307:1513-1516.

**Escalating costs can be tempered (and justified as an appropriate use of the taxpayers' dollars) if used to support interventions known to have a proven value.** However, realising these efficiencies will require systems that can provide timely access to reliable evidence and ensure that scarce resources can be redirected to practices, procedures, technologies and interventions that deliver true value for money.

**Evidence used to support any clinical intervention can only be derived from clinical trials or other outcomes-based observational data (such as data collected through clinical quality registries).** In Australia, the local generation of such evidence depends on the activity of national clinical trials networks that conduct 'public-good' clinical trials, clinical quality registries, and the specialised coordinating centres that manage clinical trials and house registry data.

> 'Australia cannot afford, nor shouldn't continue to pay for healthcare services, technologies, devices and pharmaceuticals for which there isn't a clear understanding of their comparative benefit and value.'

## Clinical Trials Networks & Clinical Quality Registries

Clinical trials networks are large collaborations of clinicians representing hospitals or community-based care facilities. They are built around a community of expert clinicians who are at the coalface of healthcare delivery and who are engaged and passionate about improving patient outcomes and healthcare productivity.

**Clinical trials networks are significantly more than the sum of their constitute parts, because:**

- Networks are broad based and representative
- They access sample sizes sufficient for statistical reliability
- They acquire expertise in the valid conduct and analysis of registry data and clinical trials
- The infrastructure, once created, can be reused at low marginal cost
- The engagement of clinicians who care for patients leads to the generation of clinically relevant research questions and analyses
- The have national or state-based coverage, incorporating regional and rural services
- They work in close collaboration with (or in some cases, have developed their own) trial coordinating centres that provide a critical mass of expertise in trials design, trial management, data management and biostatistics.

**Clinical trials networks conduct public-good clinical trials that are :**

- Not designed for commercial purposes (registration, marketing)
- Investigator-initiated and led
- Often publically funded (via the NHMRC)
- Scientifically independent and objective
- Provide definitive evidence to answer questions that are relevant to improving health
- Often closely linked to clinicians who treat patients

**The reasons for conducting public-good trials in Australia include:**

- Improving outcomes for patients involved in research
- Changing the evidence base
- Changing practice outside of clinical trials
- Addressing local patterns of care
- Increasing accessibility to new agents/devices/services
- Synergies with translational research programs around Australia
- Developing a skilled workforce
- Creating an academic environment

**Clinical Quality Registries**

Clinical quality registries capture whole-of-population data in high-significance, high-cost disease groups or therapeutic areas (eg. cardiac disease, kidney disease, prosthetic devices). They are uniquely capable of providing clinically credible data to allow benchmarking of outcomes, measurement of compliance with accepted treatments, identification and reduction of variation and a reduction of adverse events[7].

- Monitor safety and quality of products and treatments
- Determine clinical and/or cost effectiveness of treatments (including drugs, devices and procedures) across a population
- Identify differences in the quality of care across a population and monitor this over time
- Provide an infrastructure on which intervention studies can be established with relative ease
- Provide information about incidence and prevalence and its variability (over time and place)
- Identify new preventive opportunities for the disease or condition being studied.[8]

## A self-improving healthcare system

A systematic response to the now critical need to generate better evidence about the effectiveness, cost-effectiveness and outcomes of treatments provided within the Australian healthcare system requires;

**Clinical trials networks to:**

I. Generate definitive evidence through public-good trials where clinical uncertainty exists
II. Help guide effective implementation of research findings
III. Support the development of clinician-led guidelines

**Clinical quality registries to:**

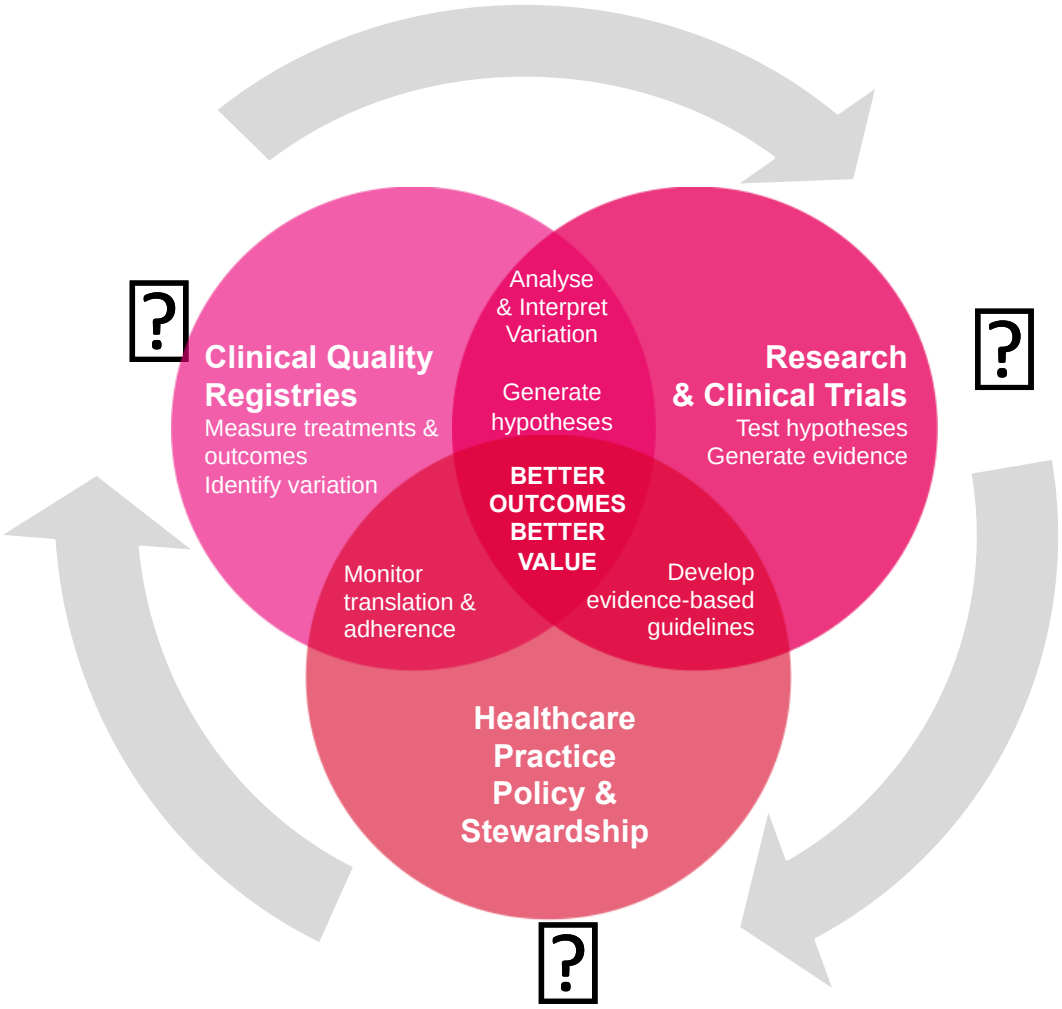
IV. Measure, monitor and report on the appropriateness and effectiveness of treatments and services
V. Identify, analyse and interpret variations in treatments and outcomes
VI. Monitor adherence to guidelines.

**Each of these is necessary but not sufficient. They are links in the chain of a virtuous cycle and all components are essential. This is our model of a self-improving healthcare system.**

Figure 1 demonstrates the virtuous cycle of improvement that is created when clinical quality registries and clinical trials are integrated as part of healthcare delivery to generate a self-improving healthcare system.

[7] Monash University Dept of Epidemiology and Preventive Medicine (2010) Funding for clinical quality registries - the Australian Cardiac Procedures Registry, Melbourne
[8] Australian Commission on Safety and Quality in Health Care, 2008. Operating Principles and Technical Standards for Australian Clinical Quality Registries

**Figure 1.**




A Self-Improving Healthcare System

## What's needed?

Cost is often cited as the most prohibitive factor influencing the conduct of more clinical trials and the establishment of registries. Clinical trials and registries are often expensive, but they don't need to be as expensive as they are currently.

Table 1. outlines a series of proposed reforms that would substantially improve efficiency and allow clinical quality registries and clinical trials networks to support a self-improving healthcare system in Australia.

## Table 1. Steps towards a self-improving healthcare system

- support the infrastructure of existing clinical quality registries that allow practicing clinicians to identify areas of important clinical variation and develop strategies to address them;
- expand the scope of clinical registries to collect risk-adjusted outcomes data across a broad range of high-cost, high-significance areas of medicine;
- provide support to develop new clinical trials networks in high-cost, high-significance areas of medicine in order to provide the key evidence where knowledge gaps are revealed by registries
- create a limited number of large-scale data management and data collection services, supported by biostatistical and health economics resources to provide economies of scale to support clinical trials and registries;
- improve the quality of routinely collected data and facilitate linkage of registry and research databases, adopting open standards for both data and systems, whilst protecting the privacy of individuals; recognizing concerns around privacy should not prevent appropriate data linkage for the public good.
- define and agree a repository of standard data elements that can be re-used within clinical trials and registries;
- establish systems that allow common treatments that are currently prescribed in a pseudo-random fashion to be randomised within a clinical trial;
- ensure that public-good clinical trials should only be required to pay for marginal costs for non-standard investigations and treatments. If a treatment or test would have been provided to a patient by the healthcare system anyway, but is utilised within a clinical trial, then the costs of the treatment or test should be borne by the healthcare system;
- conduct trials with larger sample sizes sufficient to measure critical patient-centred end-points (death and disability-free survival ) and provide these outcomes to trial co-ordinating centres via a central mechanism that utilises existing sources of administrative data;
- nest clinical trials within clinical quality registries to screen for recruitment and collect outcome data. This can significantly reduce the cost of conducting clinical trials;
- provide regulatory agencies (PBAC, MSAC, TGA) with an intermediate option (between approval and rejection) of availability of a new, unproven, treatment but only within a clinical trial or clinical quality registry;
- collect 'generic' consent at hospital admission for participation in public-good clinical trials;
- allow 'opt-out' consent for comparisons of variations of standard care that are already in widespread use such that patients may have received any one of these treatments in any case;
- simplify and standardise ethical and other regulatory approvals using a single national approach;
- make research part of the 'job description' for clinicians and ensure institutional support for that activity with protected time for conducting quality initiatives and research; and
- educate the community about unwarranted variation in treatments and the role of clinical trials and registries in providing evidence to improve outcomes

# Appendix A. Members of the ACTA Community

1. Australasian Child and Adolescent Obesity Research Network (ACAORN)
2. Australasian Consortium of Centres for Clinical Cognitive Research (AC4R
3. Australasian Gastro-Intestinal Trials Group (AGITG)
4. Australasian Kidney Trials Network (AKTN)
5. Australasian Lung Cancer Trials Group (ALTG)
6. Australasian Radiopharmaceutical Trials Network
7. Australasian Sarcoma Study Group (ASSG)
8. Australasian Sleep Trials Network (ASTN)
9. Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
10. Australasian Stroke Trials Network (ASTN)
11. Australia & New Zealand Breast Cancer Trials Group (ANZBCTG)
12. Australia & New Zealand Neonatal Network (ANZNN)
13. Australia & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database
14. Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG)
15. Australian & New Zealand College of Anaesthetists Trials Group (ANZCA Trials Group)
16. Australian & New Zealand Intensive Care Society Centre for Outcomes & Resource Evaluation (ANZICS CORE)
17. Australian & New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)
18. Australian & New Zealand Melanoma Trials Group (ANZMTG)
19. Australian & New Zealand Urogenital & Prostate Cancer Trials Group (ANZUP)
20. Australia New Zealand Gynaecological Oncology Group (ANZGOG)
21. Australia College of Emergency Medicine Trials Group (ACEM Trials Group)
22. Australian Epilepsy Clinical Trials Network (AECTN)
23. Australian Motor Neuron Disease Registry (AMNDR)
24. Australian Musculoskeletal Clinical Trials Group (AUSMUSC)
25. Australian Neuromuscular Network (ANN)
26. Australian Orthopaedic Association National Joint Replacement Register (AOANJRR)
27. Australian Paediatric Research Network (APRN)
28. Australian Primary Care Research Network (APCReN)
29. Australian Research Centre for Health of Women & Babies, Robinson Institute.
30. Bi-national Colorectal Cancer Audit (BCCA)
31. Burns Service of Western Australia
32. Centre for Anaesthesia & Cognitive Function
33. Centre for Biostatistics & Clinical Trials (BaCT)
34. Cooperative Trials Group for Neuro-Oncology (COGNO)
35. Epworth HealthCare Clinical Trials & Research Centre
36. Multiple Sclerosis Research Australia Clinical Trials Network (MSRACTN)
37. Neuroscience Trials Australia (NTA)
38. NHMRC Clinical Trials Centre (NHMRC CTC)
39. NSW Better Treatments 4 Kids (BT4K)
40. Orygen Youth Health Research Centre
41. Paediatric Research in Emergency Departments International Collaborative (PREDICT)
42. Paediatric Trials Network Australia (PTNA)
43. Palliative Care Clinical Studies Collaborative (PaCCSC)
44. Perinatal Society of Australia & New Zealand IMPACT Collaboration
45. Primary Care Collaborative Cancer Clinical Trials Group (PC4)
46. Prostate Cancer Clinical Quality Registry
47. Psycho-oncology Co-operative Research Group (PoCoG)
48. Queensland Centre for Mental Health Research
49. Queensland Clinical Trials & Biostatistics Centre
50. School of Public Health & Preventative Medicine, Monash University
51. South Australian Health & Medical Research Institute (SAHMRI)
52. Spinal Cord Injury Network (SCIN)
53. The ASPREE Study Group
54. The George Institute for Global Health
55. Trans-Tasman Radiation Oncology Group
56. Type 1 Diabetes Clinical Research Network (T1DCRN)
57. Victorian Ambulance Cardiac Arrest Registry
58. Victorian Cardiac Outcomes Registry (VCOR)
59. Victorian Cervical Cytology Registry (VCCR)
60. Victorian State Trauma Outcomes and Monitoring Registry (VSTORM)

# Appendix B. Examples of high-impact clinical trials conducted by Australian clinical trials networks

## Anaesthesia

The POISE study was a joint collaborative project with a Canadian network that enrolled over 8,000 patients having major surgery, showing that although beta- blockers reduced heart attacks, there was an unacceptable increased risk of stroke and death after surgery. This has dramatically changed practice around the world, and international guidelines have been substantially modified.

One of the most feared complications of anaesthesia is awareness or "waking up" during surgery. The B-AWARE trial of over 2,000 at risk patients proved that bispectral index monitoring reduced the incidence of "waking up" by 80%. This has been incorporated in guidelines throughout the world and use of this monitoring in Australian hospitals has grown more than 20-fold following publication of the study.

THE MASTER trial of 900 patients having major surgery identified clear pain control benefits of epidural block but no evidence of reduced serious complications. This has led to a major change in anaesthetic practice around the world, with more targeted use of the treatment, less unnecessary use, and less risk of serious complications.

## Breast Cancer

A large international trial demonstrated that the generic drug tamoxifen could reduce by 1/3 the incidence of breast cancer in women at high risk of developing the disease. The Medical Oncology Group of Australia is working with PBAC to list this inexpensive therapy for prevention, and ongoing research is developing a tool to assist GPs in identifying women at increased risk who might be suitable for this strategy.

The HERA trial demonstrated the effectiveness of trastuzumab (Herceptin) in reducing recurrence and improving survival in women with a high-risk form of early breast cancer. Since it was introduced in 2006 along with an improved chemotherapy docetaxel (proven in another trial BIG2-98, led by an Australian clinician), relapse rates have dropped significantly, saving the significant human and economic costs of recurrent disease.

## Cardiovascular Disease

The SNAPSHOT Acute Coronary Syndromes study, a collaboration between the Cardiac Society, the Heart Foundation, the Commission for Quality and Safety in Health Care and the State Clinical Networks in Australia and New Zealand recruited more than 4,000 patients from over 250 hospitals and will assist in the translation of better evidence to guide management of acute coronary syndromes across rural and regional Australia and New Zealand.

## Gastrointestinal Cancer

An Australian/Canadian collaborative trial of a biological agent used in advanced colorectal cancer demonstrated that no benefits were seen in the subpopulation of patients whose tumours contained a mutation in a critical growth gene called K-RAS, saving the PBS an annual figure of $52 million assuming all eligible patients were treated.

## Intensive Care

The DECRA trial demonstrated that a treatment that was already in widespread use in Australia, decompressive craniectomy for patients with severe traumatic brain injury (TBI), doubled the number of patients with severe neurological impairment. The lifetime cost for an individual with severe neurological impairment from TBI is in the order of $5 million. Implementing these findings will improve outcomes for people who suffer a traumatic brain injury and result in accrued savings to the Australian community of $100 to 200 million per year.

The NICE-SUGAR trial studied 6000 critically ill patients who were being treated in an Intensive Care Unit to evaluate the effect of tight control of blood sugar, which was the global standard of care at the time of the study. Contrary to expectations tight blood glucose control worsened mortality. These results mean there are now 3 fewer deaths for every 100 patients treated in Intensive Care Units.

Following the emergence of the H1N1 influenza A pandemic in early 2009, local clinicians were able to rapidly mobilise every Intensive Care Unit in Australia and New Zealand to conduct a study of all patients admitted with confirmed influenza A infection. The results of this study were published within weeks of the epidemic passing in Australia and provided valuable information to public health authorities in the Northern Hemisphere to inform preparations for the next wave of the pandemic.

The SAFE Study compared fluid resuscitation with cheap saline fluid ($1.60 / litre) compared with expensive albumin fluid ($332 / litre) and showed that the expensive fluid was not better (and actually harmful in patients with traumatic brain injury). The cost savings attributable to these results have been estimated by Access Economics to be $687 million per annum.

## Nephrology

The IDEAL trial studied 828 participants who were randomised to early or late start of dialysis and showed no difference in survival or rates of major adverse events. With the estimated cost of dialysis at $70,000 to $100,000 per patient per year, robust evidence questioning the early commencement of dialysis is highly significant in terms of clinical practice and health services planning.

Treatment of severe kidney failure, using dialysis and transplantation, costs the health system more than $1billion per year. People with chronic kidney disease have an excessive burden of cardiovascular disease. The SHARP study, a global academic collaboration, recruited 9,438 participants with chronic kidney disease, and followed them for a mean of 4.9 years to examine the effect of cholesterol lowering upon major cardiovascular events. The study demonstrated a 17% reduction in major atherosclerotic events.

The RENAL trial recruited 1,508 participants to a trial of augmented versus normal intensity of continuous renal replacement therapy in people with severe acute kidney injury and found no difference in 90-day mortality or requirement for ongoing renal replacement therapy. This has resulted in significant cost-savings as augmented therapy is twice as expensive as normal intensity therapy.

## Neuroscience

A series of trials of thrombolysis in acute ischaemic stroke including ECASS II and EPITHET, together with associated meta-analyses, led to the generation of data to support the introduction of thrombolysis as the first proven acute stroke therapy in Australia.

A series of trials of secondary prevention of recurrent stroke including antiplatelet agents and new anticoagulants for atrial fibrillation have reduced the burden of recurrent stroke in Australia.

The Australian Streptokinase Trial was one of the earliest trials of thrombolysis in acute ischaemic stroke worldwide and the first in Australia. It established that streptokinase was not the agent of choice for thrombolysis and changed the direction of thrombolytic research worldwide toward the use of rtPA (recombinant tissue Plasminogen Activator).

The PROGRESS trial tested the hypothesis that blood pressure lowering after stroke or transient ischemic attack would protect against subsequent stroke events. This proved to be the case and practice was changed world-wide as a result.

## Peri-Natal Care

The ACTOMgSO4 trial suggested that magnesium sulphate (MgSO4) given to mothers in threatened preterm labour could reduce the risk of death or cerebral palsy. This led to further research that demonstrated an 18% reduction in cerebral palsy with MgSO4 treatment. The number of mothers needed to treat with MgSO4 to prevent 1 cerebral palsied infant is 53. The cost of MgSO4 for 53 mothers is ~$160,000. The lifetime cost of 1 cerebral palsied child is $6.45 million.

The International Neonatal Immunotherapy Study showed that the increasingly common therapy of intravenous immunoglobulin [IVIG] to prevent sepsis in infants who were thought to be at high risk of infection was ineffective. IVIG did not change the sepsis rate in infants at risk of infection. This trial has avoided the global use of prophylactic IVIG, the cost for which would have been $1 billion per year.

**Each of these trials was led and conducted by Australian researchers.**
**The current cost of major trials, such as these, is in the order of $2 to 10 million.**

**These trials have improved the lives of countless Australians and are estimated to be saving our community substantially more than $1 billion per year.**