Australian Clinical Trials Alliance

Contact

Rhiannon Tate
Executive Officer

Australian Clinical Trials Alliance
Level 6, The Alfred Centre
Commercial Rd
Melbourne VIC 3004
P: +61 3 9903 0952
F: +61 3 9903 0556
M: +61 407 941 260
E: rhiannon.tate@clinicaltrialsalliance.org.au

www.clinicaltrialsalliance.org.au

Senate Standing Committees on Economics
PO Box 6100
Parliament House
Canberra ACT 2600

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Dear Committee Secretariat,

RE: Inquiry into Australia's Innovation System

The Australian Clinical Trials Alliance (ACTA) welcomes the opportunity to contribute to the Inquiry into Australia's Innovation System and to highlight to the committee the critical role of clinical research, in particular clinical trials and clinical quality registries, in improving the health and wealth of Australians.

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.

ACTA represents more than 50 individual 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. They 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 medical therapies. As a consequence they directly influence the global provision of effective and cost-effective healthcare.

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

Summary of key points

Clinical trials are an essential component of a knowledge-based economy:

1. Clinical trials are a fundamental component of the innovation 'pipeline' for health and medical discovery. Clinical trials, at the final stage of the 'pipeline', are the principal vehicle or tool to determine if an innovation actually works.

2. Many health innovations fail at the stage of final clinical testing (and after enormous investment), not because the innovation necessarily lacks effectiveness, but because of flaws in the design, execution and analysis of clinical trials. Australia is a world leader in clinical trials but this expertise is not leveraged to create the global industry leadership that is possible.

3. The investigator-led clinical trials sector shares its workforce with industry-sponsored trials that drive commercial development and, as a consequence, contributes substantially to the training and workforce development that makes Australia an attractive destination for in-bound investment in clinical trials.

Clinical trials and clinical quality registries can improve national productivity by creating better health whilst constraining healthcare spending:

4. From the perspective of a nation's wealth, the healthcare system is relevant in two countervailing ways. Effective healthcare enhances and prolongs the productivity of the workforce, but its provision is an opportunity cost corresponding to a substantial proportion of gross domestic product.

5. There is overwhelming evidence that outcomes from healthcare (i.e. the generation of health) are variable, that the effectiveness of many treatments in widespread use has not been established, and that a substantial proportion of healthcare spending is wasted.

6. The systematic application of clinical trials (to establish effectiveness and cost-effectiveness) and clinical quality registries (to monitor whether treatments are being utilised appropriately and measure patient outcomes) are the best and most rational approach to improving the quality of healthcare and reducing healthcare expenditure.

7. Such trials are most usually and most effectively conducted by networks of clinicians who understand the existing evidence base and are therefore most likely to adopt the outputs of their research findings. However, at this point in time there is minimal support for the critical infrastructure that enables these networks.

The efficiency of conducting clinical trials can be vastly enhanced if they are integrated as a routine component of healthcare delivery:

8. Clinical trials, as they are currently conducted, are often expensive- sometimes prohibitively so. This is predominantly because trials are conducted, and funded, as an activity that is separate to healthcare delivery.

9. The healthcare system can and should conduct trials as part of its 'core business' because the healthcare system provides treatments and measures (or should measure) outcomes. All that is needed to modify this to conduct trials is to create opportunities for treatments of uncertain effectiveness or cost-effectiveness to be studied within a trial.

10. Australian clinical trial networks are global leaders in creating innovative opportunities to conduct trials as a routine component of healthcare delivery.

Australian clinical trials in the global context

Australia has many advantages in the conduct of clinical trials including strong community support for clinical research, high quality clinical care, the support and engagement of clinicians, and established experience in the design, conduct, analysis, and reporting of clinical trials.

Over several decades clinical trials networks have built our position as a recognised world leader in the conduct of large, investigator-initiated, pragmatic clinical trials in several areas of medicine including cancer, cardiovascular disease, neonatology, diabetes, intensive care, nephrology, stroke and the neurosciences and anaesthesia (examples of the high-impact trials conducted by these networks are outlined in appendix B).

Many of Australia's clinical trials networks have developed strong international linkages to conduct multinational clinical trials and there is a real opportunity to increase our regional and global leadership in this area to the direct health and economic benefit of Australians.

Clinical trials and the innovation pipeline

Clinical trials are an essential link in the chain between new discoveries related to human biology and the actual creation and maintenance of good health. They are vital because they are the only valid method by which it is determined if a new treatment is safe and effective.

For the pharmaceutical and biotechnology industry they are the last critical phase of a long and costly process to bring new drugs and therapies to market. For our public research institutions, they are the bridge from frontier discoveries in basic science to clinical translation and application.

For the payers and providers of health care, concerned with getting the best outcomes for patients and the best value for the health dollar, they are the mechanism for generating evidence about the comparative effectiveness, or cost effectiveness, of different treatment options for the same condition.

However, trials are not a low value component of this chain of discovery. There is enormous, and to a large extent under-utilised, value associated with the intellectual property that is used to design, execute and interpret clinical trials. This is because these aspects of clinical trial activity can, literally, be the difference between a successful or failed innovation.

Aspects of this proprietary intellectual property that have been the focus of networks in Australia include categorisation of patient populations that can be readily identified and are most likely to benefit from a new therapy, the choice of outcome measures used to evaluate a treatment, trials designed against plausible estimates of the treatment effect size, an understanding of how a new therapy would be integrated into existing clinical care, and highly successful techniques that speed trial recruitment.

There is a global market for these skills and industry policy should be directed at creating opportunities to utilise this expertise not only for medical innovations that are developed in Australia but for those developed anywhere in the world.

A shared clinical research workforce

A recognised policy goal in Australia is to increase our nation's participation in industry-funded clinical trials, recognising that decisions about such participation are often made off-shore. The success of the pharmaceutical and biotechnology industry is reliant on a highly skilled and specialised workforce. What is perhaps not widely appreciated is the extent to which the same clinical researchers who lead or facilitate investigator-initiated trials in the healthcare system also participate in industry-sponsored clinical trials.

Clinical trials networks provide a rich framework for training and mentoring clinician researchers, trial managers and coordinators, statisticians, data mangers, epidemiologists and biomedical scientists. This workforce represents a national resource operating across the health system that provides ready-built clinical research capabilities for industry.

Increasingly, clinical trials networks are forming innovative partnerships with industry to identify and answer clinical questions of common interest that neither alone can answer.

Generating evidence to improve health and economic gain

The economic benefits arising from innovative health and medical research can be measured across four key domains.

- Direct cost savings to the healthcare system
- Benefits to the nation's productivity from a healthy workforce
- Value to society of the health gain (including quality of life)
- Benefits to the economy from commercial development

Analysis of healthcare systems suggest that as much as 30-50% of healthcare expenditure is wasted[1] A report by McKinsey Consultants[2] indicated that, in the United States, the dividends from providing the best and most efficient healthcare to all patients could be several percentage points of GDP. At this juncture, as a consequence of changes in the age distribution of the population and increasing demand and availability of new and expensive medical technology, it is vitally important to Australia's future health and wealth that the effectiveness of existing therapies, as well as new treatments, are evaluated properly within well designed studies.

The rational response to these challenges is to conduct many more clinical trials, to establish effectiveness and cost-effectiveness, and to monitor the implementation of existing and new therapies through registries that collect and analyse data on patients treated within the healthcare system. The skillsets required to generate such robust evidence from clinical trials exists in Australia- what is lacking is infrastructure and interaction between policy-makers and trialists to identify and take advantage of opportunities to improve evidence and clinical practice.

[1] Berwick DM and Hackbarth. Eliminating Waste in US Health Care. Journal of the American Medical Association. 2012; 307:1513-1516.
[2] Latkovic T. Claiming the $1 trillion prize in US health care. (http://www.mckinsey.com/insights/health_systems_and_services/claiming_the_1_trillion_prize_in_us_health_care) Accessed 31st July 2014.

Embedding infrastructure, reducing inefficiency, maximising impact

Each year in Australia there are over 9 million hospital admissions (increasing by around 6% per year), 2.4 million surgical procedures, and more than 200 million prescriptions are issued.

Despite enormous activity within the healthcare sector little is learnt about effectiveness and cost-effectiveness because only trials can be used to draw valid inference about true treatment effects and only a few tens of thousands of patients per year are enrolled in a clinical trial. Every time a patient interacts with the healthcare system and receives a treatment of uncertain effectiveness represents a missed opportunity to improve the healthcare system.

Cost is often cited as the most prohibitive factor influencing the conduct of more clinical trials. Clinical trials are often expensive, but they don't actually need to be as expensive as they are currently. ACTA proposes a series of reforms that will substantially improve the efficiency with which trials generate evidence that can be used, in turn, to improve the effectiveness and productivity of the healthcare system.

These proposals, which would embed trials as a routine and integrated component of the healthcare system, include:

- Where existing treatment options are being distributed in a random fashion establish systems by which treatments can be randomised.
- Trials should pay only for their marginal costs. If a treatment or tests would have been provided to a patient by the healthcare system anyway, but are 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 only patient-centred end-points (death and disability) and provide these outcomes to trials via a central mechanism that utilises existing sources of administrative data.
- Nest clinical trials within registries to screen for recruitment and collect outcome data.
- 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.
- Collect 'generic' consent at hospital admission for participation in clinical trials.
- Allow 'opt-out' consent for comparisons of variations of standard care that are in widespread use that the patient would have received anyway.
- Simplify and standardise ethical and other regulatory approvals using a single national approach.
- Make research part of the 'job description' for key clinicians and support that activity with protected time for conducting research.
- Educate the community about the frequency with which there is genuine uncertainty about the most effective treatments and the role of clinical trials in proving evidence.
- Support the infrastructure of existing clinical trials networks that allow practicing clinicians to identify the most relevant research questions.
- Provide support to develop new clinical trials networks in disciplines that don't currently have a network.
- Create a critical mass in coordinating centres, data management and data collection, utilising economies of scale to reduce unit prices for clinical trials and registries.

In Summary

Australia has been a world-leader in many aspects of health and medical research. Strategic investment is now critical to ensure this position is maintained and strengthened and a strong clinical trials infrastructure continues to be a major source of competitive advantage for Australia.

Maximising Australia's potential to realise societal and economic gains through innovative health and medical research requires a paradigm shift. We need to systematically generate evidence to establish the efficacy of various interventions through clinical trials, and track the appropriateness and outcomes of interventions through clinical quality registries. These activities, simultaneously, create a knowledge-based industry and improve the health and wealth of the nation.

To read more about ACTA and its role in supporting clinical trials and registries in Australia visit www.clinicaltrialsalliance.org.au

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 networks

Anaesthesia

The POISE study was a joint collaborative project with a Canadian network which 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 costs of treating recurrent disease.

Cardiovascular

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 available from this result 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. 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 saving the Australian community substantially more than $1 billion per year.