Australian Clinical Trials Alliance

IHPA Teaching, Training and Research Costing Study Public Consultation Paper December 2014

Executive Summary

The Australian Clinical Trials Alliance (ACTA) welcomes this opportunity to provide feedback to the Independent Hospital Pricing Authority (IHPA) on the public consultation paper for the Teaching, Training and Research (TTR) Costing Study. Our comments relate to the Research component of the costing study.

Key Recommendations

I. Embedded research costs should be included within the costing study.

II. The inclusion of indirect costs is supported but it is essential that costs associated with trial coordination are included and characterised.

III. Direct research costs, if identified during the costing study, should be included.

IV. The costing study should seek to understand the costs associated with research activities undertaken by staff specialists within their non-clinical time.

V. More information about precise methods should be the subject of additional consultation.

Introduction

About ACTA

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

The ACTA community incorporates 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. 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. 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).

Significance of the TTR Costing Study

Despite the many great achievements that have been made in clinical research, our current healthcare system in Australia is not as evidence-based as it should be. It continues to rely too heavily on previous experience and anecdote to drive clinical practice, and too often fails to provide treatments that have been proven to be both effective and cost-effective. Furthermore, we tackle this in the face of increasing concern about the sustainability of a rapidly escalating healthcare budget.

A key finding of the recent McKeon Review[1] was that embedding research activity within routine healthcare delivery is essential if we are to achieve the best possible outcomes for patients and safeguard an affordable healthcare system for future generations. The IHPA's work to establish the feasibility of incorporating research within the core funding architecture of public hospitals in Australia is a major step forward. However, it has long been recognised that one of the major unintended consequences of Activity Based Funding is the potential for research activities to be harmed. Reduction in research will have adverse consequences for the healthcare system as these research activities contribute substantially to improving effectiveness and productivity. We therefore believe that it is vital that this costing study is undertaken appropriately.

[1] Department of Health and Ageing (2013). Strategic review of health and medical research. Final report February 2013, 'the McKeon Review', Canberra

Detailed Recommendations

I. Embedded research costs should be included within the costing study.

One of the major challenges to understanding the costs of research activities is that many research activities, particularly clinical trials, occur as an embedded component of healthcare delivery. Clinical trials typically enrol patients that require a treatment, i.e. some treatment is non-discretionary and a treatment will have been provided by the healthcare system if the patient were not in a trial. A clinical trial randomises the patient to two or more treatment options. Particularly where a trial compares two or more types of standard care (i.e. comparative effectiveness research) the marginal cost, to the trial, of providing the treatment should be zero, as the treatment would have to have been provided by the healthcare system[2].

The costing study should evaluate the embedded costs of (at least) clinical trials for two reasons. Firstly, these data may be necessary to avoid inappropriate shifting of the costs of treatments (that are necessary and would have to have been provided anyway) from hospitals to trials. Data from the costing study may be highly useful in identifying optimal approaches to defining standard care, which can differ between hospitals. Secondly, ACTA strongly advocates that better integration of clinical trials with routine healthcare delivery has the potential to substantially improve the outcomes and productivity of the healthcare system. Any reform that results in a 'widening of the silos' of research and healthcare delivery will likely have adverse impacts on the productivity of research, which will, in turn, decrease the availability of new knowledge that would have otherwise improved the healthcare system.

II. The inclusion of indirect costs is supported but it is essential that costs associated with trial coordination are included and characterised.

It is essential that the costs of providing research support services, such as ethics committees and research governance approval, are fully characterised. One of the threats to the efficiency of clinical research in Australia is excessive delay associated with ethics and governance. There are substantial reforms underway, led by both the Department of Health and the Department of Industry to improve the efficiency of ethical and governance review. While the nature of these regulatory processes is out of scope for this study, the impact of the adequacy of resources provided for ethical and governance review are relevant. A costing study should not necessarily take into account historical costs but rather also consider the costs necessary to provide an efficient and effective service.

ACTA endorses the inclusion within the study of costs related to trial coordination. Many clinical trial coordinators are hospital employees and receive their salaries from the hospital. The costing study should identify these costs, including where there is the opportunity to recoup some of these salaries from different sources including per patient payments from both commercial and publicly funded clinical trials.

[2] Australian Clinical Trials Alliance, 2014. Submission to the National Health and Medical Council: Refinement of the standard list of items associated with conducting clinical trials in Australia: Draft final report. Available at http://www.clinicaltrialslalliance.org.au/publications/

III. Direct research costs, if identified during the costing study, should be included.

ACTA believes that the perception of the jurisdictions that hospital budgets do not contribute to the direct costs of research is incorrect. ACTA member networks are aware of many reports that the direct costs of research activity are supported, directly, from hospital budgets. This may have arisen, at least in part, as a consequence of a nomenclature issue but ACTA would regard a research coordinator/nurse that is paid directly from the hospital budget (without recoup), where that research coordinator/nurse undertakes research activities related to a trial, represents a direct research cost.

ACTA suggests that during the conduct of the costing study the consultants should remain observant for the possibility that the study may reveal examples of direct research funding (however defined). If such examples are identified, the validity of the costing study will only be maintained if these are included within the costing study.

IV. The costing study should seek to understand the costs associated with research activities undertaken by staff specialists within their non-clinical time.

Many staff specialists contribute to a range of research activities, not just clinical trials, during their non-clinical and clinical time. These are further examples of an embedded research cost. No study of hospital-based research activity will be complete if the substantial research activities that are undertaken by staff specialists during their paid non-clinical time as well as clinical time are not identified and costed.

V. More information about precise methods should be the subject of additional consultation

ACTA feels that many of the proposed activities within the costing study were not specified with sufficient depth to understand their feasibility and validity. It would be highly desirable if additional consultation with relevant stakeholders, such as senior clinical researchers within the ACTA community, were undertaken as the costing project evolves.

Once again, we thank the TTR Working Group for the opportunity to provide feedback on the proposed costing study and look forward to working closely with the IHPA to support this important program of work

Appendix A

Members of the ACTA Community

1. Australasian Child and Adolescent Obesity Research Network (ACAORN)
2. Australasian College for Emergency Medicine Clinical Trials Group (ACEM Clinical Trials Group)
3. Australasian Consortium of Centres for Clinical Cognitive Research (AC4R)
4. Australasian Gastro-Intestinal Trials Group (AGITG)
5. Australasian Kidney Trials Network (AKTN)
6. Australasian Lung Cancer Trials Group (ALTG)
7. Australasian Radiopharmaceutical Trials Network (ARTnet)
8. Australasian Sarcoma Study Group (ASSG)
9. Australasian Sleep Trials Network (ASTN)
10. Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
11. Australasian Stroke Trials Network (ASTN)
12. Australia & New Zealand Breast Cancer Trials Group (ANZBCTG)
13. Australia & New Zealand Neonatal Network (ANZNN)
14. Australia & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database
15. Australia New Zealand Gynaecological Oncology Group (ANZGOG)
16. Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG)
17. Australian & New Zealand College of Anaesthetists Clinical Trials Network (ANZCA Clinical Trials Network)
18. Australian & New Zealand Intensive Care Society Centre for Outcomes & Resource Evaluation (ANZICS CORE)
19. Australian & New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)
20. Australian & New Zealand Melanoma Trials Group (ANZMTG)
21. Australian & New Zealand Musculoskeletal Clinical Trials Group (ANZMUSC)
22. Australian & New Zealand Urogenital & Prostate Cancer Trials Group (ANZUP)
23. Australian Epilepsy Clinical Trials Network (AECTN)
24. Australian Motor Neuron Disease Registry (AMNDR)
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. Multiple Sclerosis Research Australia Clinical Trials Network (MSRACTN)
36. Neuroscience Trials Australia (NTA)
37. NHMRC Clinical Trials Centre (NHMRC CTC)
38. NSW Better Treatments 4 Kids (BT4K)
39. Orygen Youth Health Research Centre
40. Paediatric Research in Emergency Departments International Collaborative (PREDICT)
41. Paediatric Trials Network Australia (PTNA)
42. Palliative Care Clinical Studies Collaborative (PaCCSC)
43. Perinatal Society of Australia & New Zealand IMPACT Collaboration
44. Primary Care Collaborative Cancer Clinical Trials Group (PC4)
45. Prostate Cancer Clinical Quality Registry
46. Psycho-oncology Co-operative Research Group (PoCoG)
47. Queensland Centre for Mental Health Research
48. Queensland Clinical Trials & Biostatistics Centre
49. School of Public Health & Preventative Medicine, Monash University
50. South Australian Health & Medical Research Institute (SAHMRI)
51. Spinal Cord Injury Network (SCIN)
52. The ASPREE Study Group
53. The George Institute for Global Health
54. Trans-Tasman Radiation Oncology Group
55. Transfusion Research Outcomes Collaborative (TORC)
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.

In the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), 9014 Australian and New Zealand patients who had had an acute coronary event were treated with pravastatin over 6 years. Cholesterol-lowering with pravastatin significantly and cost-effectively reduced mortality and major cardiovascular events, leading to change in Australian treatment guidelines and PBS subsidy.

The recent ASPIRE trial showed that daily low-dose aspirin could prevent recurrence of unprovoked venous thromboembolism. VTE has an estimated annual economic burden in the billions in Australia, with direct health care costs of about $150 million. The cost of this trial (about A$4.5 million) is likely to be recouped within a relatively short time through savings in thromboembolism treatment costs.

FIELD was a large trial (9795 patients) which changed practice by showing that fenofibrate reduced the risk of amputation and the need for retinal laser treatment in people with diabetes. The trial acquired blood samples from all patients and thus retains a huge dataset for examining diabetes biomarkers.

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 KRAS, 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 worldwide 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.