A funding model for public-good clinical trials

The cost of clinical trials is rising but is still much less than the cost of not doing trials

Ingrid M Winship
MB ChB, MD, FRACP, Executive Director of Research[1]

John McNeil
AM, MB BS, PhD, Head[2]

R John Simes
MB BS, SM, FRACP, Director[3]

1 Melbourne Health, Melbourne, VIC.
2 School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC.
3 NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW.

john@ctc.usyd.edu.au

doi: 10.5694/mja13.10381

Clinical trials have led to significant advances in health outcomes. For example, much of the continued decline in cardiovascular mortality since 2000 has been attributed to the evidence that established the various treatment strategies now in common use.[1] However, as the costs of both medical care and clinical trials continue to rise, are our current clinical trials good value for money? In this article, the last in a series based on the *MJA* Clinical Trials Research Summit, we discuss the need for an innovative funding model for investigator-led clinical trials.

Through clinical trial evidence, treatments that are expensive yet no more effective than cheaper alternatives can be abandoned, while more cost-effective treatments or programs can be introduced. Studies casting doubt on widely practised and costly clinical interventions demonstrate the value of investigator-initiated research. Recent Australian examples include trials of vertebroplasty for osteoporotic vertebral fractures, which showed no advantage compared with a sham procedure,[2] and of craniectomy for closed head injury, which surprisingly had worse outcomes than conservative management.[3] The ENIGMA (Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia) trial showed previously unrecognised harms of nitrous oxide in anaesthesia,[4] and showed that using nitrous oxide-free anaesthesia could potentially save A$300 million per year in Australia.[5] Giving immunoglobulin to neonates at risk of infection to prevent later disability was advocated until the International Neonatal Immunotherapy Study (INIS) established that it did not make a difference.[6] Were it not for the evidence provided by such trials, many millions of dollars would be spent annually on ineffective interventions.

Just as importantly, many Australian trials have identified cost-effective treatments and preventive strategies. The recent ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism) trial showed that patients who had had unprovoked venous thromboembolism and were no longer candidates for anticoagulation could be protected from recurrence with daily low-dose aspirin, a treatment applicable to thousands of patients worldwide.[7] The cost of this trial (about A$4.5 million) is likely to be recouped within the next 1 to 2 years through savings in thromboembolism treatment costs. Lipid lowering with statin drugs has reduced cardiovascular mortality and morbidity, especially over the past decade. Its efficacy and cost-effectiveness were demonstrated particularly in the LIPID trial for patients with coronary heart disease and average cholesterol levels, leading to Pharmaceutical Benefits Scheme (PBS) subsidy of these drugs for many Australians.[8] The cost of each additional quality-adjusted life-year (QALY) related to treatment was estimated at just A$6300.[9] Evidence from this trial has improved the treatment of thousands of patients. The cost of the trial itself was A$40 million, and when the cost of treatment for patients in Australia (as a result of trial evidence) is added, the total cost equates to less than A$7000 per QALY — considerably lower than the cost of many funded health care programs.

Many potentially worthwhile studies miss out on adequate public funding, and paradoxically some of these could be undertaken at no extra cost to the health system, for example, whether 3 months of adjuvant chemotherapy for patients with colorectal cancer is as effective as the current 6 months of treatment.[10] The costs of undertaking this trial could be immediately recovered from the cost saving to the PBS.[11]

Not all trials will produce clear evidence of a benefit or harm so, in terms of value for money, the full range of trials and their results must be considered. The National Institutes of Health program of trials in stroke and neurological disorders showed that a portfolio of 28 trials costing US$335 million (a mix of positive and negative trials) resulted in more effective care being identified and implemented, at an estimated total cost of US$7700 per QALY. Clearly, such research programs and subsequent treatments represent better value for money than some of the programs our health care budget currently pays for.[12]

Can we afford to pay for clinical trials? In 2003, McNeil and colleagues suggested a budget for large-scale public-good clinical trials of A$100 million per year, which at the time amounted to 0.2% of public health expenditure.[13] By 2011, National Health and Medical Research Council (NHMRC) research grants for trials did total about A$100 million. But the cost of a large multicentre trial may exceed A$1.5–2 million per year over several years, or about twice the highest NHMRC grant in 2011. The combination of an ageing population, the increasing cost of health care and new technological advances will lead to further cost increases, making it imperative for research to identify the most effective and efficient approaches to medical care within a constrained total budget.

Another challenge in sustaining research in Australia is the cost incurred by the complexity of the regulatory environment. Ethics and governance arrangements are cumbersome, requiring time-consuming ethical and contractual procedures, complex documentation, and detailed adverse event reporting.[14] Hospitals are under pressure and increasingly reluctant to contribute to local costs of data collection. Also, clinical trials infrastructure (eg, coordinating centres available to multiple clinical trial groups) is underfunded, in spite of its potential to ultimately reduce costs.

We propose a new model for funding investigator-initiated studies. A strong clinical trial program must be embedded within and financed as part of the health system. A proportion of health care funding should be

A new funding model for achieving value for money in Australian clinical trials research

- Embed clinical trials in the health care system by linking some hospital funding to the hospital's research participation
- Deploy an additional 0.5% (rising to 1% in 2030) of total health care funding to clinical trials and health care evaluation
- Provide common infrastructure support for clinical trial networks
- Streamline clinical trials by applying regulations and reporting as in clinical care
- Set up a national body overseeing and supporting clinical trials research ◆

provided for cost-effective clinical trials for public good, as part of high-quality health care delivery, allocated on the basis of scientific quality, impact on future practice and whether a trial is expected to produce useful information. This has already begun in the United States and United Kingdom. The US academic health science centre (AHSC) model, in which institutions integrate translational research and care delivery systems, may have the potential to achieve these goals.[15,16] In the UK, the National Institute for Health Research (NIHR) has injected £1 billion into clinical and health outcomes research undertaken in National Health Service institutions.[17] The NIHR ensured, by commissioning specific projects, that research funds would not be subsumed into operations. We propose that a pool of competitive funding could support the research costs of hospitals, which would be accountable through performance indicators for the hospital executive.

In addition, sufficient funding for clinical trials infrastructure nationally would allow economies of scale in areas such as data management, project coordination and biostatistical support, an investment that would reduce the costs of future research.

We believe that an additional 0.5% of total health care funding (about A$600 million), increasing to 1% in 2030, would allow clinical research advances and improvements in health outcomes to be achieved within projected national health care costs.[18]

These costs could also be offset by steps to make trials less expensive than they are now. This would rely, first, on efficient research design, such as judicious use of surrogate outcomes and prospectively designed meta-analysis of existing evidence and, second, on relief from some of the current regulatory requirements. If trials are part of usual health care, the less onerous and less expensive legal, ethical and reporting requirements used in health care would also apply to research.

Primary health care and the private health system are important components of health care provision in Australia, and their potential contributions to effective health research should be considered.[19] Public support should also be strengthened through a concerted campaign directed at patients, encouraging them to take part in trials.

> A proportion of health care funding should be provided for cost-effective clinical trials for public good

An independent national body overseeing clinical research and evaluation, with representatives from health departments, the NHMRC and industry, is needed to lead these innovations.[20]

With this leadership, and if our funding model includes integrating trials into the health care system, financing a proportion of trials from the health care dollar and supporting investigator networks (Box), value for money in research in Australia will be within reach. If we do not do this, we will miss our opportunity for better health outcomes.

Acknowledgements: We acknowledge Rhana Pike from the NHMRC Clinical Trials Centre for assistance with the manuscript.

Competing interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed.

1 Granger CB, Murray JJ. Using measures of disease progression to determine therapeutic effect: a sirens' song. *J Am Coll Cardiol* 2006; 48: 434-437.
2 Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361: 557-568.
3 Cooper DJ, Rosenfeld JV, Murray L, et al; DECRA Trial Investigators, ANZICS Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; 364: 1493-1502.
4 Leslie K, Myles PS, Chan MT, et al. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. *Anesth Analg* 2011; 112: 387-393.
5 Graham AM, Myles PS, Leslie K, et al. A cost-benefit analysis of the ENIGMA trial. *Anesthesiology* 2011; 115: 265-272.
6 INIS Collaborative Group; Brocklehurst P, Farrell B, King A, et al. Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med* 2011; 365: 1201-1211.
7 Brighton TA, Eikelboom JW, Mann K, et al; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; 367: 1979-1987.
8 LIPID Study Group. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002; 359: 1379-1387.
9 Tonkin AM, Eckermann S, White H, et al; LIPID Study Group. Cost-effectiveness of cholesterol-lowering therapy with pravastatin in patients with previous acute coronary syndromes aged 65 to 74 years compared with younger patients: results from the LIPID study. *Am Heart J* 2006; 151: 1305-1312.
10 Chua YJ, Zalcberg JR. Progress and challenges in the adjuvant treatment of stage II and III colon cancers. *Expert Rev Anticancer Ther* 2008; 8: 595-604.
11 Zalcberg JR. Comparative effectiveness research — a proposal for a new NHMRC funding stream. *Med J Aust* 2012; 196: 22-23.
12 Johnston SC, Rootenberg JD, Katrak S, et al. Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet* 2006; 367: 1319-1327.
13 McNeil JJ, Nelson MR, Tonkin AM. Public funding of large scale clinical trials in Australia. *Med J Aust* 2003; 179: 519-520.
14 Davis ID, Chew DP. Clinical effectiveness research: a critical need for health sector research governance capacity. *Med J Aust* 2013; 198: 191-192.
15 Martin JH, Theile DE, Ho KK, Frazer IH. Diamantina Health Partners: integrating leadership in clinical research translation, education and clinical care. *Med J Aust* 2012; 196: 237-239.
16 Dzau VJ, Ackerly DC, Sutton-Wallace P, et al. The role of academic health science systems in the transformation of medicine. *Lancet* 2010; 375: 949-953.
17 Smith S. The value of Academic Health Science Centres for UK medicine. *Lancet* 2009; 373: 1056-1058.
18 Australian Government. The 2010 intergenerational report. http://archive.treasury.gov.au/igr. (accessed May 2013).
19 Nelson MR. General practice-based clinical trials. *Med J Aust* 2013; 198: 136-137.
20 Olver IN, Keech AC. Forming networks for research: proposal for an Australian clinical trials alliance. *Med J Aust* 2013; 198: 254-255. ❑