

Public funding of large-scale clinical trials in Australia

Failure to provide public funding for clinical trials may come at a high cost to the community in the long term

LARGE-SCALE MORBIDITY–MORTALITY TRIALS have become fundamental to the evaluation of most new drugs intended for long-term administration. Such trials have the unique ability to determine the net balance of positive and negative outcomes from the long-term use of drugs and allow consumers to feel confident that long-term therapy is safe in otherwise healthy individuals. A randomised controlled trial is the only study design that can provide reliable and unbiased estimates of the moderate treatment effects of interventions for most chronic diseases. Smaller studies measure surrogate outcomes or are underpowered to answer important clinical questions. If underpowered, they may be unethical and also squander the community altruism that underpins trial participation.

Large-scale trials are major logistical exercises. They involve several thousand people allocated randomly to different treatment groups and monitored for 4–6 years. Depending on the recruitment strategy and the mode of follow-up, the cost is typically \$20–\$50 million.¹ Past attempts to interest Australian research organisations in funding such studies have floundered because of this cost. In spite of this, there are a number of groups in Australia with an excellent track record in initiating and running high-quality large-scale clinical trials (many of the “public good” variety), indicating local capacity to conduct this type of research. However, these trials have largely been the province of the pharmaceutical industry. Although industry-funded studies have yielded firm scientific foundations in many areas of clinical practice, they are almost all directed towards testing superiority or equivalence of specific products, or other aspects such as greater convenience of new agents or technologies over the existing ones. Indeed, it is naïve to believe that the interests of industry will align with broader societal interests in securing effective and affordable care.²

The failure of non-industry concerns, including governments, to fund large-scale clinical trials leaves some conspicuous gaps in evidence where the consequences may be forgone savings for the public purse. In other cases, the result may be prolonged community exposure to older agents whose long-term risks have not been adequately assessed. Some recent examples highlight the importance of this problem.

Antihypertensive drugs make up a large component of the Australian pharmaceutical budget — \$516 million for the Pharmaceutical Benefits Scheme (PBS) for the newer agents in the financial year 2002–03 alone.³ For many years, there has been a trend towards these newer, more expensive agents replacing older, cheaper drugs for first-line management of mild hypertension.⁴ The justification was provided by small trials involving surrogate endpoints, such as effects on blood pressure control, vascular changes, and other risk factors. However, clinical trials with surrogate endpoints do not provide an appropriate basis to underpin long-term drug therapy: they can not provide reassurance of the drug’s long-term safety or determine the balance of desirable and undesir-

able effects of new agents. When the necessary studies of antihypertensive drugs were finally undertaken, they demonstrated that the advantage of newer agents over diuretics was marginal, at best.^{5,6}

In this instance, a lack of appropriate trial data on management of hypertension probably led to years of unnecessary expense to the PBS that greatly outweighed the cost of a large-scale trial. It is clearly in the public interest to ensure that PBS funds are not being spent on expensive therapies when much cheaper agents are just as effective. We recently estimated that the failure to provide funding for trials probably cost Australian taxpayers between \$45 million and \$108 million in 1998 alone.⁴

Another example of the false economy of failing to fund clinical trials is the recently reported Women’s Health Initiative study.⁷ Before the results of this trial were published, a generation of women was prescribed hormone replacement therapy (HRT), despite the lack of rigorous long-term safety data that could only have been obtained from a large-scale trial. There was little commercial imperative to fund such a long-term trial when large markets of regular users existed. Eventually the US National Institutes of Health (NIH) recognised the importance of funding such a study, as indeed they have funded a number of other “public good” studies. Release of the study results has led to a sharp drop in the use of combined HRT, except for short-term use to relieve significant perimenopausal symptoms. The “dividend” for the Australian government was \$16 million less expenditure on HRT in the financial year 2002–03.³

A failure to learn from these experiences may cost the community in the future. For example, low-dose aspirin is an effective antiplatelet agent whose use has recently been advocated in the United States for people with a 10-year risk of coronary events and stroke of 10% or more.⁸ This recommendation may lead to widespread use of aspirin for primary cardiovascular prevention in the elderly, despite a lack of data to indicate that its benefits in this age group outweigh the risk of haemorrhage.^{9,10} There is little likelihood that commercial interests will supply the funding to overcome this lack of data. It is more likely that industry would fund a study using a newer, more expensive antithrombotic agent in the hope of establishing it as standard therapy.

The means must be found to identify and target strategically important research questions that require public funding. A budget (in the order of \$100 million) for national research funding of these large “public good” trials should be established and administered by the National Health and Medical Research Council (NHMRC). This sum, representing 12% of the NHMRC budget and 0.2% of the recurrent health expenditure of \$60 billion, is commensurate with the importance of such trials to clinical medicine and public health. Using the NIH as a model, trials would involve a mix of requested and investigator-initiated research. Research groups, either alone or (more likely) collaboratively, would

apply for competitive funding. Although this would be administered by the NHMRC, a number of other stakeholders would benefit, including federal and state governments and their agencies, departments of health, the Health Insurance Commission, and the PBS. New funds should be made available from these sources. States should contribute to this initiative as large-scale trials are usually multicentred, allowing research capacity building and employment in both metropolitan and rural areas throughout Australia. Failure to develop a policy that supports such strategic research may well lead to waste of public funds and a delayed recognition of unfavourable risk–benefit ratios.

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1. Reid CM, Wing LM, Graham DH. A new paradigm for funding cardiovascular-outcome research in general practice. The Second Australian National Blood Pressure Study. *Med J Aust* 1998; 169: 349-350.
2. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167-1170.
3. Australian Department of Health and Ageing. Pharmaceutical Benefits Scheme. Table 10(a): Significant drug groups by highest government cost. Available at: www.health.gov.au/pbs/general/pubs/pbbexp/pbjun03/pdf/book23.pdf (accessed Sep 2003).
4. Nelson MR, McNeil JJ, Peeters A, et al. PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia, 1994–1998. *Med J Aust* 2001; 174: 565-568.
5. Wing LMH, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348: 583-592.
6. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.
7. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002; 288: 321-333.
8. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 update. *Circulation* 2002; 106: 388-391.
9. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials [comment]. *JAMA* 1998; 280: 1930-1935.
10. Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 2002; 55: 157-163. □