Impact of clinical trials on health and Australia's scientific outputs

Clinical trials are a vital link in the chain between new discoveries related to human biology and the actual delivery of good health. They are a vital link because they are the only valid method by which it is determined if a treatment is actually effective, and cost-effective, at achieving good health. Clinical trials conducted in Australia save lives, prevent disability, and produce cost-savings to the Australian community in the order of several hundred millions dollars per year. This type of research provides evidence to clinicians on how to best treat diseases of major public health importance. As such, the new knowledge that arises from these studies is immediately applicable and represents the form of investment in health research that has the shortest lag-time between inception and impact.

The funders of healthcare face dramatic challenges due to medical inflation (treatments are becoming more expensive) and impending changes in the age structure of the Australian population (the absolute number of people accessing the healthcare system will rise massively in the next two decades). A coherent strategy (indeed, possibly, the only viable strategy) for dealing with this challenge is to conduct much more clinical research. It is often not appreciated by policymakers that much of the existing corpus of clinical practice is not based on high quality evidence and that many new therapies are adopted without robust evidence that the intervention improves lives in a cost-effective way. The investigator-led clinical trials sector has the potential to play a major role in assisting policymakers to meet future challenges. Clinical trials run by commercial entities are conducted, and appropriately so, with the objective of creating profits. These studies are often conducted at high standards and provide useful information to clinicians and policymakers. However, commercial studies tend to contribute to increasing rather than controlling medical inflation. In contrast, the investigator-led sector are more likely to conduct trials that contain medical inflation. Acceptance of this argument has led to substantial real investment in comparative effectiveness research in the United States and similar investment is warranted in Australia.

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. This has translated into Australia being a world leader in the conduct of large, investigator-led, pragmatic clinical trials in several areas of medicine including cancer, cardiovascular disease, neonatology, diabetes, intensive care, nephrology, stroke and the neurosciences, and anaesthesia. Investigator-led clinical trials networks in these areas have contributed substantially to Australia's output of high impact research published in general medical journals.

Importance of clinical trials networks

The most effective way of conducting multiple clinical trials is by the establishment and maintenance of investigator-initiated clinical trials networks supported by experienced coordinating centres. This is because all of the work that is necessary to establish the infrastructure for a single trial — project coordination, sites with suitable potential participants, data management, statistical advice — is available for future trials if this infrastructure is created and sustained as part of an ongoing collaborative network. Furthermore, these networks tend to be led by clinicians, and this has two important consequences. Firstly, the research questions that these networks answer are those that are most relevant to practising clinicians. Secondly, the results tend to be implemented into practice rapidly because a community of clinician–researchers has undertaken the research and is heavily invested in implementing evidence derived from their own trials.

The well established clinical trials networks and coordinating centres in Australia face several constraints to increasing their effectiveness. These include the availability of:

- project funding and funding that is sufficient to cover the true cost of trials
- infrastructure support
- protected research time for clinician–investigators
- resources to conduct preliminary work (observational and pilot trials)
- resources to conduct high value/low marginal cost 'trial add-ons' (such as collection of biological samples, economic analyses, and work related to translation of research into practice).

It should be noted that these networks are generally constrained neither by the availability of suitable patients nor by a shortage of research questions that are relevant to public health.

Infrastructure to support clinical trials

The infrastructure required by clinical trials groups is substantial. A single trial may involve more than a hundred sites, thousands of participants, and several hundred research staff. All trials groups have a broadly similar structure and their infrastructure requirements comprise three components:

- Central infrastructure that manages the trials group
- Central infrastructure for coordination and management of projects
- Distributed infrastructure for recruitment of trial participants around the country, preferably in both city and regional areas, including where appropriate, Indigenous participants

Trials groups are generally managed by a committee that is representative of its membership. The committee sets research agendas and strategy, encourages sites to join the network, and have processes for developing and undertaking internal peer review of projects and then endorsing them as being the work of the network. *Many networks face challenges in finding the resources to maintain network organisation and governance*.

The central infrastructure for the coordination and management of projects involves experts in epidemiology and trial design, statisticians, data managers, and project managers. These individuals write protocols, recruit and train sites that will enter participants into studies, run randomisation systems, establish and maintain methods for data collection and data monitoring, and liaise with sites to ensure that studies are conducted appropriately and efficiently. This work occurs predominantly in academic departments located in university hospitals and research institutions. *Project funding, alone, is often insufficient to create and sustain this central infrastructure.*

All trials groups are critically dependent on the commitment and enthusiasm of sites that participate in their trials. Research coordinators and site investigators at these locations are responsible for recruiting patients, delivering trial interventions, collecting data, and have primary responsibility for liaising with local Health Research Ethics Committees and ensuring that trials are conducted with high ethical standards. *The availability of well trained research coordinators, with appropriate job security, is essential to the conduct of clinical trials in hospitals and the community.*

Project funding

Some investigator-initiated trials groups have been successful at obtaining NHMRC Project Grants to undertake individual projects. Although funding is often not sufficient to cover all costs associated with the project, and there is substantial cross-subsidy from academic institutions and sites that recruit participants, the funding has largely sufficed for commenced projects to be completed successfully. As such, it can and should be regarded as having been a highly successful use of NHMRC funds. *A key question is whether the relative distribution of research funds between clinical trials and other forms of medical research delivers the greatest impact on the health of Australians.*

Three aspects of the utilisation of project grant funding create constraints for these networks.

1. Project Grant process is highly competitive and some networks have found it difficult to obtain project funding due to a catch-22 situation, in which a project is not regarded as feasible until network infrastructure is established, and an effective network cannot be established without project funding. *More support to create and sustain viable networks is needed.*

2. Sometimes the infrastructure for the network is degraded between projects, necessitating avoidable additional expense and delay in rebuilding a team when a subsequent project is funded. This has been partially overcome from some networks by being successful at obtaining multiple, overlapping project grants. However, these networks often then have difficulties associated with finding resources to grow the central components of the infrastructure that need to support multiple projects. *Increased investment in clinical trials infrastructure would generate more trials, not just because there are more dollars available for clinical trials but also because more would be achieved with each available dollar.*

3. Project funding is often insufficient to cover the real costs of the trial. Projects have been completed successfully, despite incomplete funding, but do so largely by utilising the goodwill of sites, investigators, and network members. This is not a sustainable model. *Budgets for clinical trials should reflect the true costs of conducting the trial.*

Add-ons to clinical trials

The core business of the networks and the coordinating centres has been the conduct of clinical trials. However, there is the potential to add substantial value to trials, at relatively low marginal cost, by the systematic collection of biological samples, processes to optimise the translation of research into practice, and economic analysis. These additional activities are often not able to be funded as part of project funding (lest headline budgets just look too large). *A failure to support these additional activities represents a substantial missed opportunity.*

Funding to generate preliminary data

The NHMRC has funded a substantial number of phase II and phase III trials that have been completed successfully by these networks. However, the quality and feasibility of the phase II and phase III trials is often contingent on the generation of preliminary data. These include observational studies to establish incidence and outcomes, and to determine existing standard care; and pilot randomised controlled trials to determine feasibility. These research activities typically require budgets in the range of $50,000 to $200,000, but this places the studies below the range that is typically accessible via NHMRC project grant funding. *A*

competitive funding scheme to support the generation of preliminary data for clinical trials is needed urgently.

Access to electronic health data

An additional area that could also be of benefit to multiple trials groups is the capacity to access eHealth information for trial participants. Most research data for clinical trials is collected using labour-intensive analogue methods. However, there is increasing routine clinical use of hospital information systems that contain the information needed by the trial but which are difficult to access for trial purposes. *The development of information technology solutions, integrated within the eResearch Infrastructure, has the potential to substantially enhance the efficiency with which trials groups can conduct studies.*

Protected research time for clinician–researchers

The well established clinical trials networks are largely run by clinicians, many of whom have a full-time clinical load. *The availability of protected research time for these clinician–investigators, particularly mid-career researchers, is vital to the effectiveness of the networks.*

New pathways for projects conducted by the clinical trials networks

The existing funding is insufficient for the clinical trials networks to make anything other than a minor contribution to improving the evidence base for clinical medicine and providing the critical information that is needed by clinicians and policymakers to meet the challenges that the healthcare system faces. Some options for consideration are:

1. A major increase in existing funding pathways via the NHMRC

   The immediate challenges of the healthcare system will only be met by clinical trials. The lead-time from initiation to new therapeutics for basic science research is often decades. The marginal benefit from increased allocation of resources to clinical trials will be substantial. The proportion of patients enrolled in clinical trials in Australia is extremely low and there is enormous unmet need for better clinical evidence. *An increased share of NHMRC funding to clinical trials is the best strategy to improve the health of Australians.*

2. Consideration of a funding model based on the National Institute for Health Research (NIHR) in the United Kingdom

   The NIHR funding model has revolutionised clinical research in the UK. One of the core roles of any healthcare system is research, and it needs to be recognised that a portion of the healthcare budget should rightly be spent on research. This occurs in Australia, but typically funds allocated for research within the healthcare budget are subsumed within operational budgets and the research activities that are funded are often *ad hoc* and poorly coordinated. The NIHR model identifies and then undertakes centralised distribution of research funding from within the healthcare budget, acting to ensure that resources are distributed on a competitive basis to the projects with highest merit. *Consideration should be given to implementation of an NIHR model in Australia. Such a model may represent a more effective use of the resources that are currently allocated to research from within the healthcare budget.*

3. Clinical trials as an alternative to uncontrolled implementation of new clinical practices and new policy

The organisations that license drugs and therapeutics, as well as bodies that determine public subsidy for pharmaceuticals and medical procedures, face a binary choice to either approve or reject an application. Where there is evidence of effectiveness it is highly appropriate that access to new therapies be provided. However, the evidence for new therapies is often incomplete. An alternative, middle path, would be to neither reject, nor approve, but provide access to new therapies within a randomised controlled trial. If only half the patients received a new therapy, the cost-savings would be more than sufficient to cover the costs of the trial, at the end of which there would be definitive evidence of whether or not the therapy should be implemented in Australia. Additionally, healthcare policy is often implemented without evaluation, or with evaluation that comprises only a before–after comparison, which can be confounded by concomitant temporal changes. Where appropriate, new policies could be implemented within more robust designs, such as step-wedge or cluster trial, providing high quality evidence of the true impact of the policy change. *Greater engagement and partnership between policymakers and the clinical trials networks offers the potential to vastly improve the evidence base for new clinical practices and policy and to do so at low marginal cost or with actual cost-savings.*

4. Reinvestment of cost-savings from clinical trials to fund trial infrastructure

   Some clinical trials conducted by the clinical trials networks are responsible for savings to the Australian community that run into the hundreds of millions of dollars per year. These are true savings, usually arising from demonstrating that an intervention that was part of routine standard care was harmful. Examples include the use of decompressive craniectomy in patients with severe traumatic brain injury, vertebroplasty for crush fracture, and the use of nitrous oxide anaesthesia. *Consideration should be given to a process that identifies true cost-savings that arise from clinical trials conducted in Australia, with a proportion of those accrued cost-savings being made available for competitive funding for additional clinical trials.*

Evaluation of performance of the clinical trial sector

The adoption of formal targets for the clinical trial sector may facilitate its effectiveness to improve the health of Australians. Two possible targets for consideration are:

1. Proportion of patients enrolled in clinical trials

   Some spheres of medicine, such as paediatric oncology, achieve an extremely high proportion of patients being enrolled in a clinical trial. This is true integration of research and clinical practice in which the comparator arm for each trial is best established therapy. *Consideration should be given to establishing existing recruitment and then establishing targets for the healthcare system for the proportion of patients enrolled in a clinical trial with an aspirational target of 10% of all patients.*

2. Research participation as a performance indicator for hospital and Medicare Local CEOs

   Leaders within the healthcare system play a crucial role in facilitating research with direct responsibility for their institutions' approach to ethics and governance and the allocation of local resources for research, as well as indirect influence on the culture of research in their institutions. *Consideration should be given to making research participation, such as proportion of patients enrolled in a clinical trial, a key performance indicator for senior healthcare managers.*