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KEEPING CLINICAL TRIALS IN AUSTRALIA

WHY ACTION IS
NEEDED NOW

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KEEPING CLINICAL TRIALS IN AUSTRALIA: WHY ACTION IS NEEDED NOW

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KEEPING CLINICAL TRIALS IN AUSTRALIA: WHY ACTION IS NEEDED NOW

November 2011

PAPER
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KEEPING CLINICAL TRIALS IN AUSTRALIA: WHY ACTION IS NEEDED NOW

INTRODUCTION

The Australian medicines industry invests more than \$1 billion a year in pharmaceutical research and development. A significant portion of that investment is directed at clinical trials. These trials provide patients with early access to innovative medicines that otherwise would not be available. However, despite the fact that we boast some of the world's best clinical researchers and state-of-the-art infrastructure, the number of new clinical trials in Australia has been declining over the past three years by an average of 13 per cent per year.

In March 2011 the Federal Government gave the green light to a plan to reverse this alarming decline. This plan needs to be implemented urgently if Australia's clinical trials industry is to prosper.

This paper explains how clinical trials work, why new clinical trials are declining in Australia, why it is in the national interest to reverse this trend, and how implementing the Government's plan as a matter of priority could help restore Australia's international reputation as a centre of excellence for clinical trials.

WHAT IS A CLINICAL TRIAL?

“ *Clinical trials provide patients with early access to innovative medicines that otherwise would not be available* ”

A clinical trial is a formal test, or ‘trial’ of a medicine to evaluate whether it is effective for the intended uses in a medical condition, and has an acceptable level of safety.

‘Clinical’ means that the medicine is being tested or trialed in people. Before a medicine can be used in a clinical trial it must be tested in ‘pre-clinical’ tests in a laboratory environment. Only once the results of these pre-clinical tests are known can the proposed new medicine be given to people.

There are several phases of clinical trial—Phases I, II, III and IV. Satisfactory safety and efficacy must be demonstrated in each phase before the medicine may progress to the next phase. This is a brief description of each phase:

PHASE I CLINICAL TRIALS involve the first administration of the medicine to humans, usually to a small number of healthy volunteers. Phase I clinical trials determine the safety of the medicine, how it works and how well it is tolerated. These clinical trials also identify preferred routes of administration (eg tablet, liquid, injection or cream) and help determine the appropriate doses for later studies. Phase I clinical trials are usually undertaken in centres equipped for the specialised monitoring and the high degree of surveillance needed.

PHASE II CLINICAL TRIALS are normally the first trials of the medicine in patients suffering from the condition for which the medicine is intended. The principal aim of these clinical trials is to determine effectiveness and safety. These trials are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the particular disease and its treatment.

PHASE III CLINICAL TRIALS involve greater numbers of patients and are undertaken for the purpose of determining whether the medicine confers clinical benefit in the disease for which effectiveness was demonstrated in Phase II clinical trials. They also determine the nature and likelihood of any side effects. Phase III clinical trials are undertaken if the Phase II trials indicate the medicine has potential benefit that outweighs the risks.

PHASE IV CLINICAL TRIALS are undertaken *after* the medicine has been approved for the treatment of a particular disease. Phase IV trials are undertaken to compare a new medicine to a wider range of existing medicines. These trials are used to establish where in the range of treatment options the new medicine is best used.

While many clinical trials are organised and paid for by pharmaceutical companies, there are also many trials initiated by doctors, nurses, pharmacists and other healthcare professionals. This is called investigator-driven or investigator-initiated clinical research.

While the primary driver for a pharmaceutical company is to bring new products to market, companies also support investigator-driven research, both directly by providing funding or supply of the medicine, and indirectly through their financial support of company-sponsored clinical trials.

THE REGULATORY FRAMEWORK

In Australia, like many developed and developing countries, there is a strong regulatory framework for the conduct of clinical trials to ensure the safety of people who volunteer to participate in trials.

Human Research Ethics Committees

Before a clinical trial can be started a Human Research Ethics Committee (HREC) must make a recommendation that it proceeds. In Australia each HREC is constituted according to guidelines issued by the National Health and Medical Research Council (NHMRC). These guidelines mean that medical, scientific and community representatives evaluate each research proposal. More information is available about HRECs on the NHMRC website www.nhmrc.gov.au/

Informed consent

“ *Before any volunteer enters a clinical trial they must give fully informed consent* ”

One of the things an HREC will review is the informed consent process and documentation. Before any volunteer enters a clinical trial they must give fully informed consent. Volunteers receive comprehensive information about the clinical trial, written in

simple language, and have the opportunity to discuss the trial with their doctor. The HREC will check that the written information fairly and fully describes the possible risks and benefits of going into the trial, and that the consent process will be properly conducted and recorded.

Research governance in institutions

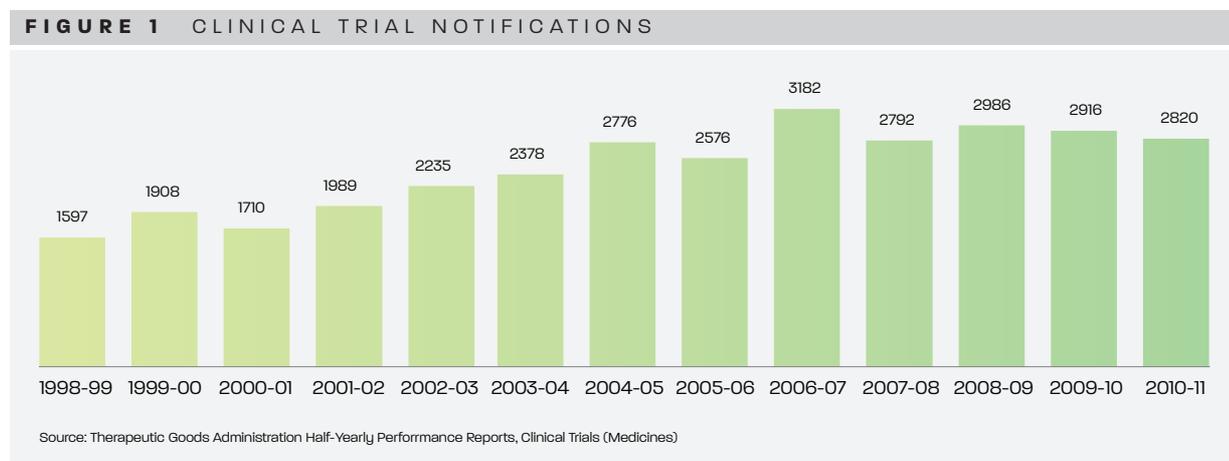
In addition to the HREC's recommendation that a clinical trial may go ahead on medical, ethical and scientific grounds, the medical institution where the trial will be run (eg a hospital or general practice clinic) must also review and approve the trial. This review takes into account the capacity of the institution to undertake the trial and ensures that necessary contractual and insurance arrangements are in place.

TGA's role

The Therapeutic Goods Administration (TGA) also has an important role in regulating clinical trials in Australia. Once a company has received HREC and governance approval, it must (with few exceptions) notify the TGA of its intention to start a trial under the TGA's Clinical Trial Notification (CTN) Scheme.

LEVEL OF CLINICAL TRIAL ACTIVITY IN AUSTRALIA

The CTN Scheme, introduced in 1991, simplified the regulation of clinical trials and allowed companies and researchers to start trials much more quickly. Since the introduction of the scheme, the number of clinical trials conducted in Australia dramatically increased, until recently, as shown in Figure 1.



The value of clinical trials

“ In 2010 alone the Australian medicines industry spent more than 10 times as much on clinical trials as the NHMRC

The medicines industry is by far the largest investor in clinical research in Australia. In 2010 alone, it spent more than 10 times as much on clinical research as the National Health and Medical Research Council, which

is the Government's principal funding body for medical research. The Australian medicines industry invests more than \$450 million a year in clinical trials in this country. Many of these trials are part of global trials, where Australia contributes data from a group of patients to the trial that may be run across 10 or more countries.

Each year more than 18,000 Australians take part in clinical trials sponsored by the medicines industry. Industry's investment in clinical trials delivers multiple benefits. It:

- ★ facilitates early patient access to new medicines
- ★ enhances the uptake of new evidence into clinical practice
- ★ improves the general standard of medical care in Australia
- ★ supports academic research
- ★ provides technical experience and global recognition to Australian researchers
- ★ helps retain talented researchers in the Australian healthcare system.

A 2006 US study of Phase III trials reported in *The Lancet* concluded: “The public return on investment in clinical trials has been substantial. Although [clinical trial] results led to increases in healthcare expenditures, health gains were large and valuable.”¹ The study looked at 28 trials with a total cost of US\$335 million, which delivered a projected net benefit to society at 10 years of approximately US\$15.2 billion.

¹ *The Lancet*, Volume 367, Issue 9519, pages 1319-1327, 22 April 2006. “Effect of a US National Institutes of Health programme of clinical trials on public health and costs”. S. Claiborne Johnston et al.

“ A dollar invested in Australian health R&D returns \$2.17 in health benefits

No such study has ever been conducted in Australia. However, a 2008 Access Economics report showed that “the projected net benefits from health R&D over the period 1992-93 to 2004-05 are estimated as \$29.5 billion, representing an average net benefit of around \$2.3 billion per year.”² The benefit-to-cost ratio was estimated to be 2.17, “which means that a dollar invested in Australian health R&D returns \$2.17 in health benefits”.³ Applying this ratio to the estimated annual industry expenditure on clinical trials (\$450 million) shows there is an economic benefit of \$977 million from clinical trials in Australia.

The Access Economics study examined benefits in terms of Australians’ health and wellbeing. But there are other benefits of clinical trial activity, including:

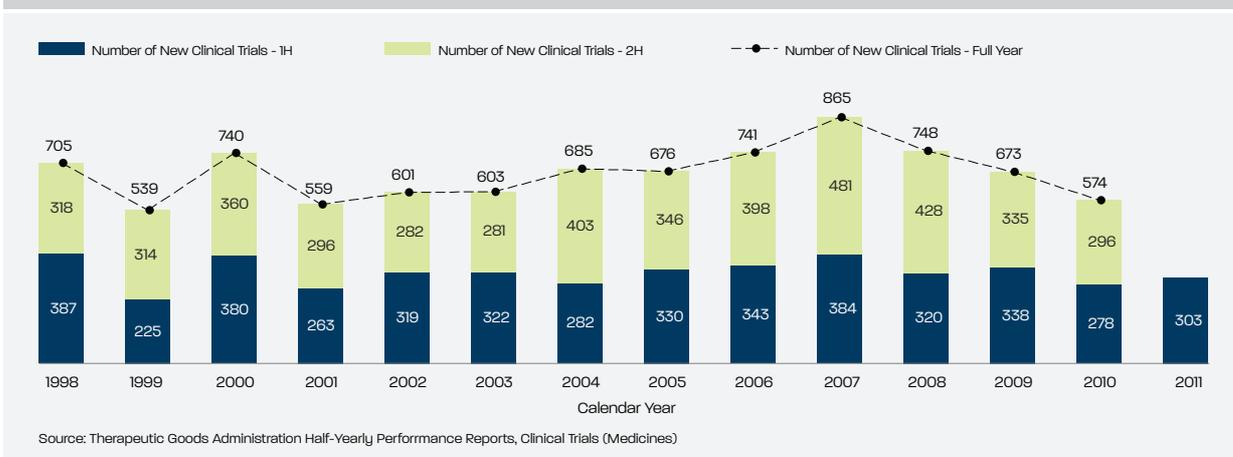
- generating investment that is deployed to academic research and supports Australian doctors, medical students and PhD candidates to pursue other research interests
- providing income to public hospitals in Australia for research activity, such as funding of hospital ethics committees (a large ethics committee in a major capital city has indicated that industry studies provide 90 per cent of the ethics committee income and yet only 30 per cent of projects considered)
- providing a valuable training ground for researchers and study staff in how to conduct high quality clinical trials, a benefit subsequently re-applied into academic clinical trials.

Importantly, running clinical trials in Australia also provides employment for many people in pharmaceutical companies and research organisations contracted to run trials on behalf of companies, and contributes to employment for researchers and their support staff in clinics.

“ Over the last three years the number of new clinical trials has declined by an average of 13 per cent per year

However, over the last three years the number of new clinical trials has declined by an average of 13 per cent per year, as shown in Figure 2.

FIGURE 2 NUMBER OF NEW CLINICAL TRIALS



It is of great concern that clinical trial activity in Australia has started to decline after a decade of steady growth. The industry has been working with the Government to investigate the reasons behind this decline and how industry, researchers and government can work together to reverse it.

² Access Economics, June 2008. “Exceptional returns: the value of investing in health R&D in Australia II.” Prepared for the Australian Society for Health and Medical Research.

³ Access Economics, June 2008. “Exceptional returns: the value of investing in health R&D in Australia II.” Prepared for the Australian Society for Health and Medical Research.

WHY IS AUSTRALIAN CLINICAL RESEARCH UNDER THREAT?

The Pharmaceuticals Industry Strategy Group, established by the Minister for Innovation, Industry, Science and Research Senator the Hon Kim Carr in May 2008, undertook a SWOT analysis as part of its work to develop recommendations to secure the future of the Australian pharmaceuticals industry. In relation to clinical trials, the analysis identified a number of industry strengths, including:

- ★ High-quality infrastructure
- ★ An ethnically diverse population, enabling trials within different ethnic groups—required by some countries such as Japan and Korea
- ★ High volunteer rate and a fast track approval system for Phase I trials
- ★ Well established track record and a high number of ongoing trials for our population size
- ★ Globally recognised clinicians
- ★ Strong and effective IP laws.

Our weaknesses in relation to clinical trials included:

- ✗ Small and geographically dispersed population—fewer patients per site and therefore higher number of trial sites compared with emerging markets. (This contributes to higher costs through lower efficiency of monitoring procedures)
- ✗ Australia's capacity to supply patients in some therapeutic areas is already stretched due to the number of ongoing trials—improved referral patterns and volunteer rates would increase capacity
- ✗ Significantly more expense for Phase II and III trials than emerging markets
- ✗ Appears less efficient—multi-centre trials require approvals from each institution.

This analysis is consistent with the experience of Medicines Australia member companies. In order to bring a trial to Australia, the Australian subsidiary of a global company must compete against subsidiaries of the same company in other countries for the opportunity to contribute patients to the global research program. Company subsidiaries in each country are compared on the metrics for cost, timeliness of trial start-up, capacity to reach recruitment targets, and the quality of trial data.

Australian companies are facing increasing competition from India, China, Brazil and emerging markets in Eastern Europe, which are high growth markets for pharmaceuticals. These countries are now attracting a larger share of global clinical trial investment because they have much larger patient populations (enabling fast patient recruitment), significant cost advantages, skilled labour and increasingly sophisticated healthcare systems to produce quality trial data.

SO WHAT ARE WE DOING TO TACKLE THIS DECLINE?

“ *Our clinical trial ethics and governance review processes are slow and inefficient*

Australia has been slow to act to reverse the decline in new clinical trials.

Our clinical trial ethics and governance review processes are slow and inefficient. In October 2006 the Australian Health Ministers' Advisory Committee recommended that Australia implement a national system in

which there would be a single ethical review of multi-centre clinical trials. This would then be accepted by all institutions where the trial will be run.

More than five years later there is still no national system in place. There are single ethics review processes now in place in New South Wales, Victoria and Queensland within each of those States. Nevertheless, sponsor companies must still obtain an ethics approval from each State as well as in each institution in every other State where the trial will be conducted.

The three eastern states recently signed a Memorandum of Understanding which will enable a single ethical review of a multi-centre trial for the public health institutions across the three states, but this does not include private hospitals or universities, which will continue to require a separate ethics review.

Clinical Trials Action Group Report

In October 2009 the Ministers for Health and Innovation established the Clinical Trials Action Group (CTAG) to develop recommendations to boost Australia's profile as a preferred destination for conducting clinical trials. The CTAG was chaired by the Parliamentary Secretaries for Health and Innovation. Membership included the Commonwealth Chief Medical Officer, a representative of the NHMRC and an industry representative. Five reference groups were established under the umbrella group to work on specific areas and report to the CTAG.

The CTAG report was submitted to the Ministers in June 2010, and released on 2 March 2011. The Report recommends:

- Speeding up ethics and governance review
- Providing for cost recovery of efficient clinical trials
- Ensuring clinical trials can take advantage of the developing e-health system
- Improving patient recruitment
- Facilitating better national coordination and greater collaboration across trial networks
- Improving reporting and monitoring of the value and performance of clinical trials and reviewing the progress and impact of implementing the recommendations.

In their foreword to the CTAG Report, the Minister for Innovation, Industry, Science and Research Senator the Hon Kim Carr and the Minister for Health and Ageing The Hon Nicola Roxon MP committed to implementing all of the report's recommendations within the timeframes outlined in the Report. At the Medicines Australia Parliamentary Dinner in March 2011, Minister Carr said:

We will work with our State and Territory colleagues to strip the inefficiencies from current application processes. We will improve collaboration between industry, researchers and hospitals. And we will explore ways to use the web to improve patient recruitment and project oversight. That work will proceed in tandem with the broader National Health Reform package.⁴

The implementation of the CTAG recommendations presents many challenges for industry, government and researchers alike. Not only is the implementation timeframe challenging, many recommendations require different stakeholders to engage beyond their primary policy imperatives.

⁴ Senator the Hon Kim Carr, Minister for Innovation, Industry, Science and Research, Speech to the Medicines Australia Parliamentary Dinner, 2 March 2011, Great Hall, Parliament House, Canberra.

One such example is the recommendation that the National E-Health Transition Authority (NEHTA) and state and territory governments make the clinical research system a key consideration when designing, developing and implementing e-health standards, specifications, strategies, frameworks, systems and programs.

This is an important consideration for the Australian medicines industry—it will enable more efficient monitoring of patients who have consented to participate in clinical trials and allow enrolment of patients from more remote locations where data capture and monitoring can be done remotely. However, up to now this has not been a key consideration for NEHTA. Accommodating clinical trials when the e-Health project is already well advanced is likely to be challenging.

GROWING AUSTRALIAN INNOVATION

“ *If Australia is to regain its position as a leader in pharmaceutical innovation, we need to act quickly to implement the micro-economic reforms identified in the CTAG Report*

There is strong evidence that global investment in pharmaceutical R&D in Australia has started to decline. Australia's competitive edge over developing and developed countries has diminished since the 1990s. Global companies are shifting their investment to countries that can start trials faster, recruit large numbers of patients quickly, and which have well trained clinicians who can produce high quality data that are cost-competitive.

If Australia is to reverse this decline and regain its position as a leader in pharmaceutical innovation, we need to act quickly and decisively, working with federal and state governments and their agencies to implement the micro-economic reforms identified in the CTAG Report.

The benefits to the economy, researchers and, most importantly, Australian patients are undeniable.

TAKING ACTION

Many people in the community aren't aware of the availability of clinical trials as an option for their care. One outcome from the CTAG Report has been delivered on time—the Consumers Health Forum has developed a *Consumer Guide to Clinical Trials*. This Guide provides useful information for consumers, including details about what kinds of clinical trials are being conducted in Australia, and where. People can visit the CHF website to access the Guide at www.chf.org.au/clinical-trials-project.php or download printable copies to distribute in the community.

However, there is much more still to be done if Australia is to recapture its reputation as a global hub for pharmaceutical R&D. It is paramount that the CTAG recommendations are implemented as a matter of the utmost urgency.

All political parties need to work constructively and collaboratively to ensure the recommendations of the CTAG plan are implemented as soon as possible. State governments, research institutes, universities, consumer groups and other healthcare and industry stakeholders all have important roles to play in supporting the implementation of these important recommendations.

There are clear health benefits and economic advantages in doing so.



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Andrew's Refrigerated Transport	KMC Health Care
Astellas Pharma	LEO Pharma
AstraZeneca	Lundbeck Australia
Baxter Healthcare	Merck Serono Australia
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