Submission
2016 National Research Infrastructure Roadmap
Capability Issues Paper

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Questions

Question 1: Are there other capability areas that should be considered?
ACTA does not believe that there are any other capability areas that should be considered but note that the critical importance of trials networks and clinical quality registries as core national infrastructure are not specifically mentioned in the section on “Health and Medical Science”.

Question 2: Are these governance characteristics appropriate and are there other factors that should be considered for optimal governance for national research infrastructure.

The Governance characteristics are appropriate but it may be helpful if these are prioritised. We would suggest that a focus on “benefits and outcomes” should be the principal driver. We feel that “Resource Management” especially with respect to skills and training should be ranked as the second most important priority.

In addition, in order to ensure that policy positions such as the ones articulated in this application occur, peak bodies also require support so that evolving and innovative concepts can be applied within a broad national health and science agenda.

Question 3: Should national research infrastructure investment assist with access to international facilities?

In the field of “Health and Medical Science”, much of the knowledge base required to improve health and medical outcomes depends on international collaboration. Such collaboration is key to complementing areas where Australia has strengths such as the development of specific products (medicines, vaccines, diagnostics). Hence, funding criteria need to encourage innovative international partnerships with academia, the philanthropic sector and industry. In the case of healthcare, the heterogeneous nature of complex clinical conditions, confounded by a mix of environmental and genetic factors as well as co-morbid conditions, necessitates an international approach to improving health outcomes. We see such collaboration as critical, provided that Australia continues to play a key leadership role in such collaboration (see Q4).

Question 4: What are the conditions or scenarios where access to international facilities should be prioritised over developing national facilities?

Whilst many improved health care outcomes have and will result(ed) from international efforts, it is critical that sufficient infrastructure exists in Australia for Australian clinicians to participate as equal members of international consortia. Not to do so, risks deskilling the clinical workforce, losing the opportunity to leverage Australian discoveries in fundamental research and delaying translation of new research findings from these international efforts into clinical practice, due to lack of engagement of Australian opinion leaders in the process of testing new concepts. Notwithstanding the limited infrastructure support,
Australians are global leaders in the creation and development of effective and cost-effective infrastructure for trials networks and registries. There is much that Australia can provide to the rest of the world.

In addition, much health and medical research in Australia must out of necessity, address uniquely Australian issues embedded in the specifics of our own health system.

**Question 5:** Should research workforce skills be considered a research infrastructure issue?

ACTA believes that research workforce skills are a critical component of research infrastructure. With respect to the role of the national clinical trials networks, the co-ordinating centres that support them and clinical quality registries as critical core infrastructure, these are virtual, horizontally distributed structures that are completely dependent on the research workforce. The skills, knowledge, experience and training of these clinical personnel leveraged off the fact that these staff are embedded in day-to-day clinical practice, are an essential component of this research infrastructure.

**Question 6:** How can national research infrastructure assist in training and skills development?

Clinical trials networks, the co-ordinating centres that support them and clinical quality registries provide a natural mechanism for junior or less experienced staff to realise the innumerable opportunities that such virtual/soft infrastructure brings to the health care system. Within the clinical trials networks for example, there are multiple opportunities for junior clinical staff to be involved in the design, conduct, analysis, interpretation of clinical trials and ultimately participate in vital translation of new research findings into practice.

**Question 7:** What responsibility should research institutions have in supporting the development of infrastructure ready researchers and technical specialists?

Whilst research institutions such as Universities provide essential undergraduate and post-graduate training in health-related sciences e.g. medicine, nursing etc, as well as non-health sciences eg. engineering, mathematics, computer sciences etc., it is simply not possible for such institutions to offer undergraduate or post-graduate students the insight or skills required for the conduct of large phase 3 randomized clinical trials or engagement with national quality registries without strong links to the clinical research networks. Whilst these groups may be based in Universities, they function as semi/independent entities linked as much to clinical practices and the hospital sector as to Universities.

**Question 8:** What principles should be applied for access to national research infrastructure, and are there situations when these should not apply?

In the case of clinical trials networks, co-ordinating centres and quality registries, the key principles that need to underpin their function when in receipt of public funds, is that the data are owned by the clinical network or clinical registry that are governed in an appropriate and transparent manner and that the proposed research initiatives whether through a clinical trial or analysis of registry data, addresses an important clinical question. In the case of a quality registry, these need to comply with the national Framework developed by the Commission of Safety and Quality in Health Care (1).

**Question 10:** What financing models should the Government consider to support investment in national research infrastructure?

In order to fund the clinical trials networks, co-ordinating centres that support these networks and the quality registries, it is likely that a central agency will need to be established (if an appropriate central agency does not already exist). The role of such an agency would be to prioritize funding initiatives, develop measurable milestones for achievement and translation into practice, allocate funds accordingly,
monitor progress and facilitate inter-governmental relationships in order to maximize the opportunities such funding affords.

**Question 12: Are there international or global models that represent best practice for national research infrastructure that could be considered?**

The National Institutes of Health (NIH) in the US and the National Institute of Health Research (NIHR) in the UK have all established clinical trials networks and co-ordinating centres to facilitate their clinical trials endeavours. In the case of the NIH, it referred to clinical research co-ordinated through networks as the “linchpin of the nation’s biomedical research enterprise” (2).

In the case of the UK, over £1 billion annually has been invested in infrastructure to establish and, co-ordinate clinical trials networks and translate the results of these efforts into routine clinical practice. A study in Sweden conducted by the Boston Consulting Group indicated that an investment of $70 million in clinical quality registries would result in a 13% reduction in health-related spending (the estimated cumulative return equalled over $7 billion in reduced health costs over 10 years (3).

In the case of non-commercial studies, it is possible to conduct trials without the clinical trials networks such as those developed in the UK and the USA (and endogenously, but all too often, not sustainably in Australia), but such trials are highly inefficient (i.e. the cost per study completed/patient recruited is very substantially higher without the virtual infrastructure created by the trial network). In addition, there is a substantial opportunity cost in the number of studies that can be done by ‘established’ networks and an even greater opportunity cost for trials that are desperately needed to optimize health outcomes, but can’t be done in Australia because the required clinical trial network doesn’t exist (e.g. mental health, cardiology etc).

**Health and Medical Sciences**

**Question 15: Are the identified emerging directions and research infrastructure capabilities for Health and Medical Sciences right? Are there any missing or additional needed?**

The current National Research Infrastructure Capability Issues paper, under the title of “Health and Medical Sciences”, does not address the key role of clinical trials networks, the co-ordinating centres that support them and clinical quality registries as core national infrastructure essential in delivering improved health outcomes for the Australian population.

The wealth of any nation is predicated on the health of that nation. After years of investment in biomedical science, Australia, as part of the developed world, is on the cusp of transforming the many scientific discoveries and learnings from clinical and biological research (as diverse as behavioural science to studies of genomic prediction of disease) into a much healthier and hence much wealthier nation.

However, with the costs of healthcare expected to inexorably double to over $250 billion over the next three decades (4), it is more critical than ever that changes in clinical practice are based on firm evidence. Evidence that not only proves that new practices or new drugs and devices are superior to previous approaches, but as importantly, that current practices deduced from historical observations but often not based on robust proof, provide value for money.

Whilst such a policy position will be obvious to everyone, the capacity to achieve such expectations requires a fundamental understanding of the complexity of the multitude of illnesses that afflict society, as well as insights into how health care delivery occurs not only in the management of chronic diseases, but
also in the management of acute conditions (such as traumatic injury, surgical procedures, management of serious conditions during pregnancy, end of life care, etc).

Diseases we once considered simplistically as malfunction of a single organ, or atypical altered health states (such as pregnancy) actually represent a plethora of heterogeneous, multifactorial conditions that not only have different manifestations based on their cause, but can be very substantially modified by other illnesses, as well as ancillary medications at one end of the spectrum through to the underlying genetic make-up of the affected individual at the other.

Equally, the management of acute clinical conditions such as patients in intensive care, patients undergoing major surgical procedures, the management of difficult pregnancy are ever more complex, as we develop greater understanding of the various factors that may impact on determining clinical outcomes.

An understanding of this complexity means that the generation of firm evidence through clinical trials - the most effective tool to develop a new evidence base, often based on national if not international collaboration, requires an understanding of the key clinical questions to be addressed, a clear plan of how to translate the results of such trials into clinical practice and the collection of real world data through clinical registries (see fig 1) to understand the impact of such research in the “real world”.

Figure 1; The self-improving health system
Clinical trials are the key tools required to demonstrate that new is better than old, or that previously accepted practices are (or are not) useful. However, because of the many factors outlined above, the development pathways for new treatments have become more and more complex. To bring a new to market, requires a much more sophisticated approach to ensuring that the clinical and economic value of such a discovery can be understood and critically appraised as to whether it represents a true advance warranting taxpayer support than ever before. Similarly, the capacity to ask whether an existing practice delivers the benefits claimed, not only requires the evidence base to link real-world practices to outcomes via a clinical registry, but an informed, trained workforce that can translate uncertainty in the real world (outside of trials) into a clinical question or hypothesis that can in turn be addressed using clinical trial methodology (see fig 1).

A potent solution to challenges resulting from the inherent complexity in the conditions to be treated as well as the delivery of effective and efficient health care in the context of the many social, industrial and political issues that impact on the capacity of the workforce to deliver new knowledge, is to empower discipline-specific or disease-related clinical research networks that encompass clinical trial networks as well as the co-ordinating centres that support their work and clinical quality registries that measure translation into practice, to navigate this minefield. Such structures are virtual entities, bringing together all the individuals working in a particular area for the purpose of improving healthcare. The clinical research networks then become the vehicles that because of their capacity to draw nation-wide on knowledge and experience in a specific discipline (eg. Intensive care, anaesthetics, paediatrics, etc.), or a specific disease (eg. cancer, kidney diseases etc.), can harness the expertise to:

1. Understand the illness or condition in question.
2. Understand the evidence base that underpins current practice.
3. Understand the determinants of current approaches to management.
4. Understand the limits of current knowledge.
5. Understand international practices and emerging trends.
6. Prioritize key areas of clinical uncertainty.
7. Understand how to address and resolve the clinical questions that such information provides
8. Understand how the results of such research are most efficiently translated into routine clinical practice

With this background, it is clear that these organisations:

1. Represent key infrastructure required to determine standards of care against which new approaches need to be evaluated and their impact measured.
2. Represent key infrastructure to determine areas of uncertainty in current clinical algorithms which warrant further evaluation.
3. Represent key infrastructure to link the real world with opportunities to improve healthcare outcomes and through exploration of the value of scientific discovery.

In 2011 (5), the NCRIS Roadmap in considering “Translating Health Discovery into Clinical Application”, under the heading of “Infrastructure requirements” recommended

“to enhance the capacity to perform clinical trials, a dispersed model has been suggested centred on groups with disease and trial specific expertise. The infrastructure required is support for clinical trial networks, such as research staff, statistics services, tissue banks and information systems to support randomization, data capture and analysis”

Unfortunately, this recommendation was not funded although the importance of data and soft infrastructure as part of the national framework was recognised. However, the need to support these
structures is greater than ever before. If we wish to create true clinical and economic value from medical research, if we wish to extend the areas of influence of such models into key areas in which Australia lacks effective national networks such as mental health, musculo-skeletal diseases, cardiology etc., if we wish Australian research to participate in the global efforts to create meaningful value from the fruits of fundamental research and thereby extend the reach and influence of such scientific discovery to improve practice both nationally and internationally, if we wish to help translate the impact of our investment in education and science including key related sciences like bioengineering, biostatistics, health economics, etc, into clinical and economic value, if we wish to empower our fledgling biotechnology sector through links between the discovery and commercialisation worlds, it is critical that we recognise the pivotal role the clinical research networks, co-ordinating centres and registries, play as core national infrastructure.

Although Australia has a number of internationally acclaimed clinical trials networks and national clinical quality registries (6), the existence of such networks and their achievements as well as their role as potential instruments of change in practice for the common good has ‘slipped under the radar’. The Executive Summary and Highlights of the “Activities & Achievements of Clinical Trial Networks in Australia 2004-2014” report (6) is attached. In addition, several other sections of this report, outlining achievements to date, are appended (see Appendix 1). There is a very substantial opportunity cost in not taking advantage of such existing key infrastructure to address the challenges of 21st century health care and a very significant opportunity cost in not leveraging this model across more of the health system. At the same time, through NCRIS support, there is an extremely valuable opportunity to lead the world in a systematic, science led, consumer directed approach to the health and wealth of Australians.

The National Institutes of Health (NIH) in the US belatedly ‘discovered’ the importance of such national networks some years ago in a paper entitled “Re-engineering the clinical research enterprise” (2), describing clinical research as “the linchpin of the nation’s biomedical research enterprise”.

*The paper suggests that the NIH will “create a roadmap to re-engineer the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field of scientific discovery....*

*Furthermore, the paper continues, “although biomedical research has succeeded in converting many diseases once considered uniformly lethal into more chronic, treatable conditions, it has become clear...that the US must recast its entire system of clinical research...the exciting basic discoveries...demand that clinical research continue and even expand... “*

*“At the core of this vision is the concept that clinical research needs to develop new partnerships amongst organized patient communities, community-based physicians and academic researchers... In these initiatives, NIH will promote the creation of better integrated networks of academic centres that work jointly on clinical trials and that include community-based physicians who care for sufficiently large groups of well-characterized patients...”*

*Similarly, the NIH Roadmap recognizes the importance of the clinical research workforce “...to make further progress in controlling major human diseases, we must cultivate and train a cadre of clinical researchers with skills commensurate with the increasing complexity and needs of the research enterprise...”*

*“An enriched pipeline of biomedical discoveries ...” requires “large studies which are best conducted through networks of investigators who are equipped with tools to facilitate collaboration and information sharing.”*
“This effort will promote and expand clinical research networks that can rapidly conduct high-quality clinical studies that address multiple research questions. Best practices can then be identified and widely disseminated, further enhancing the efficiency of clinical research networks.”

Although the focus of the NIH Roadmap is predominantly based on translating biomedical discoveries into health improvements, Australian clinical researchers, industry and Government have a much more sophisticated understanding of what is required to co-ordinate a national approach to improving health. Not only do many Australian trials networks supported by a relatively small number of co-ordinating centres and clinical registries, already exist (6) but our networks have long understood that asking ‘how we improve health outcomes’ not only means a focus on the discovery of new approaches, translating new biomarkers into new and much more effective drugs, developing new devices, vaccines or diagnostics, etc. but as importantly, it also means validating current therapies that contribute so much to the burden of an increasingly costly, but not necessarily increasingly efficient, health care system.

With the knowledge that investment in clinical trials conducted by clinical trials networks and clinical quality registries deliver at least a 5-fold return-on-investment (ROI) in direct health costs (7), we must grasp this opportunity provided by the NCRIS Roadmap. We must act on the fact that the clinical trials networks, co-ordinating centres and associated clinical registries:

- Represent “critical national research infrastructure needed to underpin future research and innovation capability in health related sciences and medicine (8)“.
- Represent “world-class research infrastructure capability which urgently needs support for both existing and emerging groups for future strategic development (8)”.
- Desperately “require capacity building for the strategic benefit of Australia’s overall research effort (8)”.
- Currently “lead international trends and best practices, but without investment, risk Australia’s national research clinical networks failing to deliver on the world-stage (8)”
- Must “sit strategically within Australia’s National Science and Research Priorities and other Government priorities, creating collaboration within the research system both nationally and internationally and with the users of research such as business and industry (8).

We must act on the realization that such networks represent core national infrastructure.

We must not let the fruit whither on the vine.

References:

7. Clinical Trials Networks and Clinical Quality Registries - the value proposition. (unpublished data, Australian Commission for Safety and Quality in Health Care)
Participating Networks

Australasian College for Emergency Medicine Clinical Trials Group
Australasian Gastro-Intestinal Trials Group
Australasian Lung Cancer Trials Group
Australasian Radiopharmaceutical Trials Network
Australasian Sarcoma Study Group
Australasian Society for Infectious Diseases Clinical Research Network
Australasian Stroke Trials Network
Australia & New Zealand Breast Cancer Trials Group
Australia & New Zealand Melanoma Trials Group
Australia New Zealand Gynaecological Oncology Group
Australian & New Zealand Children’s Haematology/Oncology Group
Australian & New Zealand College of Anaesthetists Clinical Trials Network
Australian & New Zealand Intensive Care Society Clinical Trials Group
Australian & New Zealand Urogenital & Prostate Cancer Trials Group
Australian Epilepsy Clinical Trials Network
Australian Musculoskeletal Clinical Trials Group
Australian Paediatric Research Network
Australian Primary Care Research Network
Cooperative Trials Group for Neuro-Oncology
Multiple Sclerosis Research Australia Clinical Trials Network
NSW Better Treatments 4 Kids
Paediatric Research in Emergency Departments International Collaborative
Paediatric Trials Network Australia
Palliative Care Clinical Studies Collaborative
Primary Care Collaborative Cancer Clinical Trial Group
Psycho-Oncology Co-operative Research Group
The Australasian Consortium of Centres for Clinical Cognitive Research
The Australasian Kidney Trials Network
The Australasian Sleep Trials Network
The Spinal Cord Injury Network
The Australian Type 1 Diabetes Clinical Research Network
The Interdisciplinary Maternal Perinatal Australasian Collaborative Trials Network
Therapeutic and Vaccine Research Program, Kirby Institute
Trans Tasman Radiation Oncology Group
Executive Summary

Australia is regarded as a world leader in the design and conduct of high impact investigator-initiated clinical trials. Often referred to as ‘public good trials’, these studies are conducted in the absence of commercial interest and are designed to answer important clinical questions, providing unbiased scientific evidence to help consumers, clinicians and policymakers make decisions about which treatments, tests and services are most effective or offer the best value for the healthcare system.

Generating the level of evidence needed to reliably inform clinical practice or healthcare policy requires large collaborative clinical trials that are conducted across multiple centres and involve many hundreds or thousands of participants, healthcare practitioners and researchers. In Australia, and throughout the world, clinical trials networks (sometimes referred to as clinical trials groups or collaborative trials groups) have been formed as a means of bringing together a large community of clinical researchers with a common interest in advancing the evidence base for a particular area of clinical practice. These multidisciplinary collaborations result in horizontal and vertical networks of clinical research leadership, expertise and capacity that are integrated within the healthcare system.

Over the last 25 years, the number of clinical trials networks within Australia has steadily grown, along with the recognition that networks are a vital component of both a high-quality healthcare system and a strong and competitive clinical trials enterprise in Australia, which includes commercial and public good trials. However, our understanding of this unique component of our clinical trials sector – in terms of what networks exist, how they are formed and sustained, and the scope and impact of their research – and how best to support and enhance the vital work undertaken by clinical trials networks, has been limited. In 2014, the National Health and Medical Research Council commissioned the Australian Clinical Trials Alliance to report on the activities and achievements of Australia’s clinical trials networks over the last decade. A comprehensive survey of national or state/jurisdiction-based clinical trials networks was undertaken with the aim of describing the structure and core functions of networks and capturing a detailed snapshot of studies completed and published, or currently being conducted, by networks within the last 10 years.

There were 37 clinical trials networks identified in Australia of which 34 contributed data for this report. These networks span a wide range of clinical disciplines and disease groups and incorporate upwards of 10,000 clinical researchers across the country – the majority of whom are practicing clinicians. Whilst the formation of most networks was driven from within a clinical community, these groups uniquely bring together clinical experience with a broad range of expertise in trial design and conduct, including research coordination, project management, data management and biostatistics. There were networks actively researching across all levels of the healthcare system – including acute, sub-acute and primary care or community settings and, importantly, the majority undertake trials in sites throughout rural and regional Australia as well as the major metropolitan centres.
There was a wide range of activities reported to be 'core functions' undertaken by the networks surveyed, but common among almost all networks was a key role in supporting the collaborative development of research proposals and a process of internal peer review of study proposals and protocols to ensure scientific merit and rigour. Despite the size of their membership and the scope and significance of their research within the health system, networks by and large have relatively low levels of central infrastructure, which, in part contributed to the incompleteness of data used in this report.

Collectively, the clinical trials networks participating in this study have published in the last 10 years, or are currently undertaking, more than 1,000 studies that involve 10 million participants or will involve participants close to one million participants. The vast majority of these studies were phase II, III or IV clinical trials and whilst many involve multinational collaboration, more than half were designed and run by Australian investigators. The total estimated amount of research funding reported for these studies was more than $1 billion, which included public and private funding generated from within Australia and overseas.

Australian clinical trials networks have made a substantial contribution to the global evidence base across an array of different conditions. More than 100 high-profile studies that have directly influenced clinical practice and/or healthcare policy – both within Australia and internationally – were reported. Networks have also been highly successful at forging partnerships with investigators overseas to conduct multinational clinical trials, and these relationships are particular strong with Canada, the United Kingdom, the United States and France.

Whilst this report suggests that a substantial proportion of Australia’s clinical research effort has come from clinical trial networks over the past decade, it is likely that these figures are a significant underestimate of true activity. This is due to major limitations in the amount of data that networks were able to provide (largely attributable to limited resources or that could be sourced from public records. For some figures, this could be as much as half of the total amount reported. Furthermore, where studies involved international collaboration, the portion of total recruitment and total funding that arose from within Australia could not be determined.

Major data limitations were also encountered when attempting to accurately determine the relative proportion of clinical trials networks activity to total clinical trial activity in Australia. A conservative estimate is that over the last 10 years, network trials have received at least one third of all funding awarded by the National Health and Medical Research Council for clinical trial-related activity during this period, and around half of the funding awarded for grants for clinical trials with budgets that exceeded $1 million.

Data from the Australian and New Zealand Clinical Trials Registry and ClinicalTrials.gov indicated that networks may have undertaken at least one quarter of the large non-industry trials (trials with a target sample size of more than 1,000 participants) conducted in Australia in the last decade. However, this could not be accurately determined and the finding supports the well-recognised need to develop mechanisms that facilitate collection and reporting of accurate data of clinical trials activity in Australia. This applies particularly in relation to investigator-initiated trials where both public investment and participation in these trials is considered an essential underlying component of our healthcare system.

This landmark report provides a unique and valuable snapshot of the activities and achievements of clinical trials networks in Australia. It highlights that clinical trials networks have made an immense contribution to the clinical evidence base across numerous clinical disciplines. However, it also points to the fact that there are high disease-burden areas of the health system, that do not have a nationally coordinated clinical trials network currently. It is also likely that existing networks would achieve substantially more for the public good if they had access to better infrastructure and additional funding. It is hoped that this report will serve as a basis to inform future research, policy development and investment to maximise the capacity of Australian clinical trials networks, and a benchmark against which to evaluate the future impact of these efforts.
Key Facts AT A GLANCE

COLLECTIVELY

34 clinical trials networks that participated in this study represent more than 10,000 healthcare practitioners and researchers.

Networks undertake a range of different activities but have the common core function of enabling the collaborative development and internal peer-review of research proposals.

Networks are extensively integrated with acute and sub-acute hospitals as well as primary and community care facilities across all jurisdictions and into regional and rural areas of Australia.
The total number of studies published by networks per year appears to have more than doubled between 2004 and 2014.

Australian clinical trials networks have together completed and published or initiated more than 1,000 studies in the last decade, representing more than 1 million participants and at least $1 billion in total research funding (possibly much more).

Networks have been established across a wide range of clinical disciplines and disease groups, but there are still areas of high disease-burden that don’t have a nationally coordinated clinical trials network, such as heart disease, mental health and asthma.
Key Facts AT A GLANCE

Networks have variable (and predominantly limited) capacity to report their aggregated research inputs and outputs or to report recruitment in near real-time. This may be attributed to the fact that these networks have relatively low levels of central infrastructure and employ a median of only 1.9 FTE per network.

There are more than 100 examples

- Change Practice
- Change Policy

Of prominent clinical trials published by networks in the last decade that have had, or are expected to have, a direct impact on clinical practice and policy.

Networks have developed extensive global partnerships to undertake multinational trials, but more than half of their studies are designed and led by Australian investigators.
It is currently impossible to accurately determine the proportion of clinical trial activity within networks to total clinical trial activity in Australia. A conservative estimate is that networks undertake approximately 7-19% of all non-industry clinical trials, and

**ONE QUARTER OF LARGE NON-INDUSTRY CLINICAL TRIALS WITH A SAMPLE SIZE >1,000 PARTICIPANTS CONDUCTED IN AUSTRALIA**

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The median interval between the date of first funding of a network trial by the NHMRC and publication of the primary results is only 5 years.

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It is currently impossible to accurately determine the proportion of NHMRC funding for clinical trials that has been received by networks. A conservative estimate is that studies undertaken by networks account for approximately one third of all NHMRC funding awarded for clinical trial-related activities since 2000, and

**APPROXIMATELY HALF OF THE FUNDING AWARDED FOR LARGE CLINICAL TRIALS WITH BUDGETS GREATER THAN $1 MILLION.**
1 Introduction

1.1 Background

1.1.1 Clinical trials

Clinical trials enable the testing of hypotheses that are concerned with evaluating the effectiveness, efficacy or cost-effectiveness of a biomedical intervention (including preventive measures, treatments, clinical strategies, and diagnostic tests) in patients. They are a fundamental component of the process of generating evidence to inform clinicians, health consumers, and policymakers about the most effective and cost-effective ways of preventing, diagnosing and treating ill health and improving health outcomes. Clinical trials are an essential link in the chain of translation and also drive innovation. In general, the evidence obtained from randomised clinical trials defines international best practice for the treatment of any disease, health condition or clinical discipline. Hence they form the basis of international or national clinical guidelines that inform state of the art, high-quality healthcare.

Novel treatments are usually developed through a process that exploits fundamental knowledge of a biological mechanism to develop a new intervention that is be expected to result in a health benefit. However, the experience of decades of clinical research is that some such interventions are ultimately proven - via well-conducted randomised clinical trials - to be either ineffective or actually harmful. These trials use well-established scientific methods that are necessary to achieve validity and reliability for a given result, but they are not foremost an ‘academic’ exercise. Rather, clinical trials are a practical and pragmatic means of providing reliable information that for individuals, helps save and improve lives, and for society, helps to inform the most valuable use of scarce health resources.

1.1.2 Who conducts clinical trials?

Although there can be some overlap, clinical trials are broadly categorised into those conducted by two groups: Commercial entities such as pharmaceutical companies or clinical research organisations; and clinical investigators working within the healthcare system or based within a public academic institution such as a university. These are hereafter referred to as commercial clinical trials and investigator-initiated clinical trials:

**Commercial trials** are conducted by organisations that typically own or have a financial interest in the intellectual property related to the intervention being tested. Commercial organisations use the information obtained from the trial for many reasons including to support regulatory applications to obtain licenses to sell their products, to support applications for private or public subsidy of the cost of providing the product, and to support marketing the product to clinicians, patients, and Governments.

Trials that are conducted to support regulatory applications are often designed in conjunction with regulatory agencies such as the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMEA). These trials provide valuable evidence to support the licencing of new products or procedures, but they do not always provide answers to all of the questions that are relevant to the introduction of the new intervention into clinical practice. This may be because the commercial trial was conducted in a highly specific population and clinicians are left uncertain about whether the results can be extrapolated to other groups of patients, the trial evaluated the intervention under ideal rather than
routine or ‘real-world’ circumstances or because the comparator group may not be relevant to usual clinical practice.

**Investigator-Initiated Clinical Trials** are trials that are conceived and conducted by independent clinicians and academic researchers. These trials serve the broad purpose of generating clinical evidence to improve health care (where that evidence does not exist) rather than for a commercial imperative.

### 1.1.3 What are investigator-initiated clinical trials?

Investigator-initiated clinical trials provide a public good. These are trials that address clinically relevant research questions that are important to clinicians, patients and policymakers. They advance the public good because they seek to identify the best intervention, irrespective of its commercial relevance. Examples of investigator-initiated trials include the evaluation of:

- licensed products to replicate the results of commercially conducted trials;
- licensed products but within a pragmatic design that tests the effectiveness of the product as used in routine clinical practice rather than in tightly controlled circumstances;
- licensed products in patient groups that extend beyond those used in commercial trials to establish additional areas in which a product may be helpful (off-label trials);
- new uses for old drugs that are no longer on patent;
- two or more types of standard care, irrespective of whether standard care involves a licensed product (comparative effectiveness research);
- clinical algorithms or protocols that combine multiple components related to diagnosis and treatment or both (process-of-care trials and systems-of-care trials); and
- non-drug and non-device biomedical interventions.

### 1.1.4 Benefits of investigator-initiated trials

Investigator-initiated trials have often been used to demonstrate, that widely adopted components of standard care for many diseases were either ineffective or harmful. An example of an advance in medical care that arose from investigator-initiated public good trials was the discovery that aspirin, a drug that was almost 100 years old, was highly effective at reducing death in patients with an acute myocardial infarction (1).

Some investigator-initiated trials will also have commercial relevance because they evaluate some aspect of a commercially provided intervention. However, investigator-initiated trials are conducted by investigators who are conducting trials independent of any commercial organisation or the commercial relevance of study outcomes.

The extent to which clinicians can call upon evidence derived from well-conducted clinical trials to guide their practice varies substantially between disciplines. The dramatic improvement in survival that has occurred in many forms of childhood cancer, particularly leukaemia, is a consequence of embedding trials within routine clinical practice so that new chemotherapy regimens were serially tested against best known current treatments resulting in massive iterative improvements in outcome (2). However, there are many other disciplines of medicine, including anaesthesia, intensive care, infectious diseases, neonatal medicine, nursing, physiotherapy, and surgery, where only a small proportion of clinical decision making can be guided by evidence derived from well conducted clinical trials. Where there is insufficient evidence,
patients and policymakers are left uncertain as to the most effective and cost-effective interventions and
this paucity of evidence often promotes unwarranted variation in clinical care (3). Investigator-initiated
trials play a vital role in enhancing the evidence base, particularly when there is no commercial imperative
for the evidence to be generated.

1.1.5 Clinical trials networks

Whilst clinical trials are just tools in the development of a self-improving health system, they are
nonetheless complex and require considerable methodological expertise (such as in statistics,
epidemiology, and data management) and training. They may also require a large number of patients to
participate in a clinical study in order to identify relatively small but significant health gains. Hence most
investigator-initiated clinical trials are conducted by groups of clinicians in collaboration with the
appropriate experts. The involvement of clinicians serves to maximise the likelihood that the questions
being prioritised are those that are most relevant to improving clinical practice.

A clinical trials network, also known as clinical trials group or a collaborative trials group, is an organised
group of clinicians and other researchers who share infrastructure that enables them to collaborate to
conduct multiple multicentre clinical trials. Clinical trial networks exist throughout the world and their
number is increasing progressively. These networks are both horizontal and vertical in that they involve
researchers and sites that conduct trials that are geographically dispersed. Some networks are restricted to
a city or a state, others are national or international, some are global, but all involve multiple healthcare
centres and are virtual in that they don't require buildings, laboratories or equipment used in areas of basic
research. In many diseases and clinical disciplines, these networks of clinicians have formed close
 collaborations with people with relevant methodological expertise in order to efficiently conduct and
coordinate both small and large clinical trials.

Clinical trials networks have the potential to create innumerable synergistic interactions - that is, their sum
is substantially more than their constituent parts. The constituent parts are: the sites that enrol patients
into trials; investigators that plan, conduct, analyse, and report trials; and central trial coordination and
data management. Synergies of efficiency that facilitate the conduct and quality of trials conducted by
networks include:

- The network is a community of clinicians and other researchers. The community has a shared sense
  of challenge and achievement associated with the conduct of trials. The individuals who provide
  leadership for a network are responsible for, and representative of, their community, which has a
  shared mission and vision to generate high quality evidence that improves patient care in a
  particular discipline or field of medicine.

- Networks provide the capacity to generate trials with larger sample sizes. Many trials need to
  recruit thousands of patients to have sufficient statistical power to demonstrate small but highly
  clinically relevant effect sizes. Networks provide a larger number of sites, working together on the
  same study, addressing the same question because of its clinical importance and in this manner,
  often facilitate greater recruitment that non-network trials.

- Networks have the capacity to conduct multiple sequential trials, with new trials starting as old
  trials complete, sometimes informed by the results of the earlier study. This means that research
  coordinators (or research nurses) who recruit patients, help deliver interventions, and collect data
  at individual sites, can be employed across multiple projects. Similarly research staff employed
  within the networks can be retained to more efficiently move from one project to the next. This
  lowers the marginal cost of conducting trials but also ensures that experienced research personnel
do not need to be recruited and trained for each new trial. It is this collective workforce of clinical research personnel at the level of sites and within clinical trials networks that forms part of the essential infrastructure required for this type of research.

- Networks are horizontally devoted with the only requirement for sites to participate being that they treat or see patients who are suitable for inclusion in the networks' trials. As such, networks tend to have sites in non-teaching as well as academic institutions, and have sites in rural and regional locations as well as metropolitan locations. This also allows the evaluation of interventions across the full range of locations in which the results would be implemented into actual clinical practice. This feature substantially enhances the external validity of trials – that is, the results of trials are more likely to apply to all patients than just patients seen in tertiary centres.

- Networks have shared intellectual infrastructure; the knowledge and expertise associated with the design, conduct, analysis, and reporting of clinical trials is shared among all the investigators in the network. Networks often undertake extensive internal peer-review of trial plans and manuscripts before they are submitted for funding applications and publication, respectively. This allows the networks to maximise the validity, feasibility, and impact of the trials that they conduct and also ensures a greater chance of funding due to the quality of the study design.

- Networks often own or utilise shared infrastructure that is necessary for the central management of trials including project management, data management, and appropriate statistical analysis. They also can facilitate the development of standardised study tools, for example, the definitions of variables used for entry criteria and evaluation of outcome, which promotes comparability across studies.

- The network infrastructure, once created, is preserved for future trials. Stand-alone trials, conducted outside a network, must recreate the infrastructure for each new trial. This allows networks to conduct more trials and recruit more participants per dollar of public funding.

- Over time, networks develop a brand that arises as a consequence of the shared track record of the network. This 'brand value' gives confidence to journal editors, funding bodies, and guideline developers about the quality of trials conducted by the network. Networks are highly invested in ensuring the success and quality of all projects because their brand value is dependent on creating and maintaining the highest possible standards. Such 'branding' is almost certainly likely to lead to increased international collaborations which not only allows clinically important questions to be addressed more quickly, but also brings novel ideas and products not otherwise available to Australians through the clinical trials networks.

- Although it has never been evaluated empirically, it is highly likely that the results of trials conducted by networks are translated more rapidly into clinical practice. This 'in-built' translation arises as a consequence of the participation of a diverse and extensive group of clinicians in the design and conduct of the trial. Having done the trial, they are more likely to believe the findings and thus become highly incentivised to implement its findings into their own clinical practice.

- While clinical trial networks are independent of industry, this does not preclude their collaboration with industry. Where the interests of both a network's researchers and a commercial entity are aligned, this allows sharing of resources, expertise, and infrastructure to conduct trials.

- Clinical trials networks generally establish an array of relationships that greatly enhance their effectiveness and efficiency. These key partnerships include relationships with academic organisations, such as Universities and Medical Research institutes (MRI), Colleges that undertake training of medical specialists, special Societies that represent the interests of clinicians as well as consumer and advocacy groups associated with specific conditions. This spectrum of relationships vastly enhances the effectiveness and impact of the work conducted by networks.
1.2 The value of clinical trials networks

1.2.1 The funding & policy landscape for clinical trials in Australia

Clinical trials are expensive. Many of the highest value Project Grants that are awarded by the National Health and Medical Research Council (NHMRC) are used to conduct investigator-initiated clinical trials. The resources utilised by networks to conduct trials can be divided into resources that support the central infrastructure of the network and the resources that are used to conduct specific clinical trial projects. In turn, the resources used to conduct specific clinical trials projects can be further divided into those that support the central project coordination and those that support the direct costs of participant recruitment, delivery of an intervention, and collection of data at the site or practice level.

The central infrastructure of the network represents the component that supports the collaborative development of trials but not expenditure on direct trial conduct. Network activity involves both paid staff and volunteers. However, most paid staff involved in network activities are not employees of the network but rather are employed by Universities or MReis (predominantly to undertake central trial coordination), or by hospitals (for example, to recruit participants, deliver interventions, and collect data). As such, networks often have a range of key partnerships with Universities, MReis and hospitals, as well as Clinical Societies and Colleges, some of which host and support networks. The role of volunteers, and the goodwill of both volunteers as well as paid staff, cannot be underestimated as a critically important resource that is harnessed by networks to facilitate their work.

1.2.2 Why this report is timely and important

There are a number of initiatives at various levels of Government that in some way aim to improve the research capacity of investigator-initiated clinical trials networks: either through direct central infrastructure support for networks; access to platform technologies; improving the efficiency of trial processes including those related to ethical and governance regulation; better funding models for clinical trials; and enhancing collaboration and coordination between networks.

Despite the importance of networks in generating high-quality evidence to inform practice and policy, and the fact that clinicians participating in the work of these networks do so on a daily basis as part of their routine clinical roles in order to improve healthcare outcomes, relatively little is known about the composition, size, activity, impact, and sustainability of the investigator-initiated clinical trials sector in Australia. There is limited understanding about how Australian networks have been formed, developed, structured and sustained; the volume and type of trials completed and underway; the major outputs of networks; how many clinicians and researchers are engaged; and where clinical trials expertise does and doesn’t exist across disease and discipline groups. Similarly, the proportion of investigator-initiated clinical trials that are addressing health issues for specific patient populations within Australia and the level of cross-discipline or international collaboration that exists are not known.

A better understanding of clinical trials network activities will be an invaluable resource to inform key stakeholders about clinical trial capacity, identify where new networks could be supported, drive decision making to enhance the sector, and serve as a benchmark against which the impact of initiatives to enhance the sector can be evaluated.