## AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE





# The National Clinical Trials Governance Framework

Literature review



Australian GovernmentDepartment of Health

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Overview of the Australian approach to clinical research governance

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## **Document structure**

The Australian Commission on Safety and Quality in Health Care (the Commission) has undertaken a review of the literature on clinical trial governance frameworks as a key deliverable of the contract with the Australian Government Department of Health (the Department) to develop a national Clinical Trials Governance Framework (the Governance Framework). This document includes the following sections:

- Section 1 provides a summary of the literature review report and key findings
- Section 2 provides the background and the context of the Governance Framework project
- Section 3 contains a detailed description of the literature review methodology, and the findings from the international and Australian peer-reviewed and grey literature, including insights from New Zealand, the United Kingdom, South Korea, Canada, the United States of America, the European Union and the Nordic region
- Section 4 focuses on current approaches to clinical trials governance in Australia and three developed countries, as required by the contract: Canada, the United Kingdom and South Korea
- Tables detailing reviews, recommendations and report listings (Tables 7, 8, 9 and 10) are provided at Appendix 1. A comprehensive list of Australian policies that guide clinical trial operations, together with government and non-government reports are provided at Appendix 2.

# **Section 1: Review summary**

# Key messages

The purpose of this literature review is to identify approaches to clinical trial governance that have been highlighted within the literature as leading to an improved clinical trial environment.

Over the last two decades several countries – including Australia, New Zealand, Canada, the United Kingdom, the European Union and the United States of America – commissioned or conducted high-level reviews into the clinical trials sector. This action was prompted by shared or similar concerns regarding:

- The loss of competitive advantage in the clinical trials sector
- Increasing competition from low-cost, highly populated countries such as India and China
- Perceptions of a concomitant decline in clinical trials activity, particularly commercially sponsored trials
- Operational and administrative burdens which were perceived as detrimentally affecting the cost, quality and efficient conduct of clinical trials.

Where a national approach to clinical trials governance was implemented, the literature suggested a consolidated action plan at the national level leveraged the capacity and interests of all key stakeholders and enabled the coordination of common solutions, as has been achieved in the UK and in South Korea. Successful national approaches are coordinated by a government-supported entity and underpinned by guiding polices, legislation and infrastructure.

The literature review has identified approaches to clinical trial governance that have resulted in improvements in the clinical trial environment. Key components of successful approaches as have been achieved in the UK and in South Korea to clinical trial governance include:

- A national strategic plan for change with clearly articulated guiding principles for the implementation of a governance framework, realistic objectives and measurable outcomes
- A national (or bi-national, as in the EU) legislation and policy framework
- A national or central coordinating agency
- A national or central IT platform
- A national and local site-capability framework
- National independent accreditation to assess local-level providers to confirm they have implemented the nationally harmonised approach to clinical trials governance.

## Introduction

A review of the academic and grey literature was undertaken to provide evidence on governance frameworks for clinical trials in Australia and internationally, with focused insights from three developed countries. The narrative review method is used to present the broad perspective on clinical trials governance with reference to historical issues, and approaches to addressing these issues in current clinical trials governance frameworks. The search strategy included both the peer-reviewed literature (such as published, peer-reviewed journal articles) and grey literature, so that published and unpublished reports, policy documents and relevant materials could be included.

English language reports in human research and publications related to clinical trials and governance between 2007 and January 2018, and commentary on the governance of clinical trials at the hospital and/or funding health agency level, were included. Research and reports published prior to January 2007 of in-vitro or animal studies, and those that did not include commentary on the governance of clinical trials at the hospital level and/or funding health agency level, were excluded from the review.

## Method

Keywords that guided the search terms for the academic literature were determined after reviewing medical subject headings (MeSH) from the US National Library of Medicine and subject headings for CINAHL and the Health Policy Reference Centre.

The key question guiding the review was: What mechanisms exist, or are recommended, for clinical trials governance at the hospital level, and/or funding health agency level in Australia and internationally?

Sub-questions were also developed including:

- 1. What clinical trials governance mechanisms exist, or are recommended?
- 2. What are the key components of these mechanisms?
- 3. What are the stated rationales for the use of these mechanisms?
- 4. What are the barriers and facilitators to implementing the identified mechanisms?
- 5. What evidence is there for the impact of these mechanisms?

The search strategy of the peer-reviewed literature covered a range of study designs including: randomised controlled trials, controlled clinical studies, guasi-experimental designs, descriptive studies of programs, pilot studies, conference papers, reviews and commentaries. All titles, abstracts and full-text articles where available were retrieved. The reference lists were hand-searched to ensure the review was comprehensive. If papers were found that had not previously been identified the titles and abstracts were then reviewed. If these additional papers met the search inclusion criteria, they were also retrieved and stratified using the PRISMA method (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

In total, 513 articles were identified as being potentially relevant to the literature review. A further 21 articles were identified through snowballing from the reference lists of relevant articles, forward citation searching and author searches. After the removal of duplicates and those records not meeting the inclusion criteria, a total of 66 papers were included in the final review.

A purposive search strategy of the grey literature provided published and unpublished reports, policy documents and relevant materials obtained from a variety of sources, including websites of government departments and private companies.

Critical review of the grey literature was undertaken by two reviewers. A total of 285 records were located through the grey literature search. Of these, 76 records were included in the literature review as well as information extracted from 70 websites. The grey literature search identified several high-level reports from a number of countries including Australia, Canada, New Zealand (NZ), the United Kingdom (UK), the United States of America (USA), South Korea, the European Union (EU) and the Nordic region. An Endnote database was established to organise and store the journal articles and the grey literature, and to manage references and citations.

There were no empirical studies published in the peer-reviewed literature describing or evaluating governance frameworks for clinical trials. The literature predominantly focused on the commercial and clinical benefits of conducting clinical trials, current constraints of the clinical trial operational environment, and possible solutions to incentivise the environment.

The grey literature search comprised a review of policy documents and reports of clinical trials governance processes from Australia, New Zealand, UK, USA, Canada, South Korea, the Nordic region and the EU. Synthesis of the international grey literature enabled comparisons of guiding policies and clinical trial governance frameworks (either implemented or proposed), and the evaluation of these frameworks in countries with similar systems of government and organisation of health services as Australia. As a result, the countries of focus for this review include the UK, Canada and South Korea.

# Key findings

Over the last two decades several countries – including Australia, New Zealand, Canada, UK, EU and USA – commissioned or conducted high-level reviews into the clinical trials sector. This action was prompted by shared or similar concerns regarding:

- The loss of competitive advantage in the clinical trials sector
- Increasing competition from low-cost, highly populated countries such as India and China
- Perceptions of a concomitant decline in clinical trials activity, particularly commercially sponsored trials
- Operational and administrative burdens which were perceived as detrimentally affecting the cost, quality and efficient conduct of clinical trials.

The academic literature is predominantly descriptive case studies and/or commentary, and discussion focused on quantifying costs and the time taken to obtain ethical approval for multi-centre clinical trials. The organisational and administrative barriers to conducting clinical trials, particularly pertaining to ethical/regulatory review, have received the most scholarly attention.

Where a national approach to clinical trials governance was implemented, the literature suggested a consolidated action plan at the national level leveraged the capacity and interests of all key stakeholders and enabled the coordination of common solutions, as had been achieved in the UK and in South Korea. Successful national approaches are coordinated by a government-supported entity and underpinned by guiding polices, legislation and infrastructure.

Conversely, it was clear that developing policies and processes without a centralised strategic approach was less likely to be effective. For example, the Canadian Clinical Trials Coordinating Centre (CCTCC) failed to align initiatives under way in the provinces in order to realise the benefits of a nationally coordinated approach. Similarly, in the EU, legislation was not uniformly implemented by member nations which led to increased inefficiencies and brought to bear the understanding that '…if legislation intended to strengthen harmonisation is not carefully implemented, it can become counterproductive to its aims'.[2] The type of healthcare system, and the motivation and priorities of health decisionmakers, had the greater influence on the success of initiatives to improve the clinical trial environment. For example, Australia, Canada, the UK and South Korea have singlepayer systems that facilitate the centralised management of clinical trials, whereas the USA health system is fragmented and predominantly a fee-for-service, user-pay model, which impedes the implementation of a national approach. An illustration of this point is provided in the summary of approaches to the governance of clinical trials in the UK, Canada, South Korea and Australia.

Key components of successful clinical trials governance frameworks identified include:

- A national strategic plan for change with clearly articulated guiding principles for the implementation of a governance framework, realistic objectives and measurable outcomes
- A national (or bi-national, as in Europe) legislation and policy framework
- A national or central coordinating agency
- A national or central IT platform
- A national and local-site capability framework
- Independent accreditation to assess local-level providers to confirm they have implemented the nationally harmonised approach to clinical trials governance.

Several authors have identified other factors that could be considered for developing a national clinical trials governance framework including:

- Publication of statistics on ethics and localsite approval processing times with national benchmarks. Statistics would focus on the efficiency and speed of the processes required to initiate and complete a clinical trial (such as time to ethics approval, contract completion and research participant recruitment rate versus expected) [3]
- Development of a research governance system that provides mandatory staff education and project monitoring throughout the course of the research project to improve clinical research practice [4,5]
- Mandatory Good Clinical Practice accreditation for all clinicians involved in clinical trials and research more broadly [6,7]
- The establishment of an organisation to oversee, regulate and streamline disparate arrangements for ethical approval and to provide a new national research governance service

- The requirement for national accreditation or certification of local researchers and credentialing of external researchers using standardised criteria. Voluntary clinical trial-site accreditation has improved the efficiency and quality of clinical trials, just as the accreditation of hospitals has been used to improve safety and quality in health care. Authors also note that carefully constructed and judiciously governed accreditation systems can reduce the burden and expense of clinical trials on trial sites. Evaluating the impact of accreditation criteria on costs and quality are critical to creating the appropriate system [3]
- Consistency across jurisdictions and across the public and private sector in relation to local-site approval. This consistency is best found at a national level [8] to support a single rigorous review by a reputable national group that is accepted by private and public hospitals, research institutes and regulators [9]
- The provision of incentives, through funding agreements for health services to engage in research support and measures of research operations performance for health service administrators [10]
- The integration of research into routine healthcare [10] to foster a research culture in health organisations [11], and encourage health administrators to recognise the research activities occurring in their institutions [12]
- The implementation of a risk-adapted approach to the regulation of clinical trials [13]
- The mandatory requirement for all clinical trials to be registered on a publicly available website with publicly available summary results and information on trial outcomes [14]
- Clearly articulated performance metrics for domains within an accreditation standard (that consider infrastructure, investigator and team, site management, study management, data management, continuous quality improvement and the care of research participants).[15,16]

A centralised, single-entry point for ethical and governance review with mutual acceptance across hospitals, universities and research institutions has been effective in the UK, South Korea and elsewhere to streamline the ethicsapproval process. Similarly, a research passport system [17] has been implemented in the UK as an honorary research contract for researchers who do not have a contractual relationship with the National Health Service (NHS). The research passport aims to remove the need for researchers working across multiple NHS sites to obtain an honorary contract from each research site.<sup>1</sup> However, it has been disputed that research passports have streamlined the process, as the passport application process can be extremely lengthy, with researchers waiting up to nine months to receive passports to begin clinical research.[18]

The development and harmonisation of clinical trial operational standards and more effective use of electronic health records to assess clinical trial study feasibility, facilitate patient recruitment, and streamline data collection at baseline and follow-up [19] have been implemented successfully in the UK and South Korea.

The literature review also highlighted the work that is occurring in the clinical trials standards and accreditation space by organisations such as TransCelerate<sup>2</sup> and the Society for Clinical Research Sites.<sup>3</sup> These organisations have already developed site-qualification and training tools to facilitate mutual recognition of certain investigator and site capabilities across some companies. The Alliance for Clinical Research Excellence and Safety has also embarked on an international stakeholder consensus process to create global standards for accreditation of research sites (the Site Accreditation and Standards Initiative).

While several countries have undertaken reviews into clinical trial operations, each country has responded to the findings from their respective reviews in different ways. Further, each country has proposed or implemented approaches to improve their local clinical trials environment, depending upon government policies and priorities and available funding and resources. The following provides a summary of approaches to the governance of clinical trials in Australia and in the countries of focus in this review: Canada, the UK and South Korea.

## **United Kingdom**

The UK has significantly invested in the implementation of a governance framework for clinical trials and health research. The overarching governance framework comprises several interlocking elements including a centralised and streamlined ethics-approval process; a suite of resources and services designed to support and facilitate research at the local level; metrics to measure and benchmark performance which is tied to funding arrangements; and clearly articulated stakeholder roles and responsibilities. The framework is underpinned by legislation (Care Act 2014); the UK Policy Framework for Health and Social Care; the Research Support Services Framework with standard operating procedures for NHS organisations and an operational capability statement which is owned by the organisation's board. This places research and clinical trials specifically on the health service delivery agenda of the hospital or research organisation.

The UK has implemented its governance framework for clinical trials and health research through a designated body, the National Institute for Health Research (NIHR). The NIHR was established in 2006 and is funded through the NHS. The NIHR is responsible for a large portfolio of health research activities covering infrastructure, funding, research faculty or support, and systems. These responsibilities are managed through a national coordinating centre which is responsible for central management, information technology, the portfolio<sup>4</sup> database, workforce development and training, oversight of patients, consumers and the relationship with industry.

The NIHR operates the clinical research networks (CRN) in 15 locations, through which clinical trials are managed and conducted. In order to retain commercially sponsored trials in the UK, the objective of the NIHR-CRN is to promote patient equality of access to participation in a clinical trial, to streamline ethics and governance approvals and cost structures, and to performance-manage the NHS to ensure the timely and efficient conduct of eligible clinical trials. This includes streamlined administrative procedures associated with regulation, reporting and approvals of clinical trials, and the integration of clinical trials into clinical care. A key feature of the UK clinical trials reform program is that initiatives are underpinned by legislation (Care Act 2014) and supported by a governance framework (the UK Policy Framework for Health and Social Care Research); an operational framework (the NIHR Research Support Services Framework [Research Support Services Framework]); a research and development operational capability statement; guiding policies and standard operating procedures which are underpinned by standard documentation.

The Health Research Authority (HRA) was established on 1 January 2015 as an executive non-departmental public body sponsored by the Department of Health under the Care Act 2014.<sup>5</sup> The HRA was viewed as the most efficient and effective way to deliver the improvements required, by providing coordination and oversight across the UK. The HRA has several core responsibilities including the National Research Ethics Service which comprises research ethics committees (REC) and the Integrated Research Application System (IRAS).

HRA approval provides the unified approval for all clinical research in the NHS in England and was fully implemented in 2016. The HRA approval system brings together the assessment of governance and legal compliance which is undertaken by dedicated HRA staff with the independent ethical opinion provided through the UK Research Ethics Service based on the submission of only one application.

The primary policy framework is the UK Policy Framework for Health and Social Care Research v3.2 2017 (UK Policy Framework).[20] The UK Policy Framework sets out principles and responsibilities at a high level and takes into account relevant legislation in the UK. At the local trust (hospital) level, the local policy framework outlines the responsibilities and accountabilities of both individuals and organisations involved in research at a high level. This includes chief investigators, research teams, funders, sponsors, contract research organisations, research sites, regulators of professions, other regulators, employers, and health and social care providers. At the local level, the UK Policy Framework documents the relationship between principles of good practice in managing health and social care, and the responsibilities of individuals and organisations.

The Research Support Services Framework does not specify 'who' undertakes specific roles (local trust, NIHR, CRN etc.) but it identifies those activities for which the organisation is accountable. The purpose of the Research Support Services Framework is to support proportionate management and governance of research. The Research Support Services Framework provides guidelines for NHS organisations to develop a set of consistent and streamlined standard operating procedures for all types of studies, including clinical trials. It also describes specific tools to implement these standard operating procedures including the research and development Operational Capability Statement and the study planning tools.

The NIHR standard operating procedures (SOP) and dependency framework aligns with the Coordinated System for NHS Permission (CSP) and its implementation using the Research and Development Management Information System. The Research Support Services Framework contains SOP templates, the research and development Operational Capability Statement, and guidelines for participating organisations and sponsoring organisations.

Organisations use and maintain a research and development operational capability statement which is a board-approved statement of agreed research and development operating principles (as part of the organisation's research and development readiness). The statement puts research and development on the agenda of the Board and raises the profile of the research and development office in managing operational risks on behalf of the organisation. It also provides a mechanism for reporting progress and escalating research and development governance issues that cannot be addressed through normal business practice.

## Canada

A central feature of Canada's approach to a national solution for the governance of clinical trials has been the establishment of a government-funded, central coordinating agency charged with actioning the recommendations arising from high-level reviews across the clinical trials sector. While the Canadian Clinical Trials Coordinating Centre (CCTCC) has successfully implemented several programs designed to improve and strengthen clinical trials and promote Canada as an attractive clinical trials destination, it has been unsuccessful in facilitating a pan-Canadian approach to harmonising, streamlining and centralising the clinical trial ethical review process. In the absence of strong national leadership, provinces have independently progressed initiatives designed to improve the efficiency of ethical review at the local level. The Canadian experience has particular resonance for Australia. Australia could consider creating synergies between jurisdictional initiatives and a national approach to avoid the duplication of effort and resources and to ensure a common goal for revitalising the clinical trial sector.

The CCTCC was established in 2014 following the 2011 Canadian Clinical Trials Summit. Recommendations arising from this summit were shaped into a strategic action plan that was intended to guide initiatives focused on incentivising the environment. The first recommendation was to establish a national headquarters, the CCTCC, to oversee and enable the remaining recommendations designed to strengthen the Canadian clinical trials environment.

The national framework for conducting research involving humans is the Tri-Council Policy Statement for Research Involving Humans developed by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada (the Policy). The Policy provides guidance on the interpretation of the principles of research ethics and serves as a benchmark for the ethical conduct of research involving humans across Canada. There are several mandatory requirements for researchers, institutions and members of research ethics boards and adherence to the policy is a condition of funding for those researchers and organisations that receive funding.[21]

A major focus for Canada has been to centralise, harmonise and improve REB efficiencies at the pan-Canadian level. Currently, there is no centralised or single-entry point to lodge ethics applications although initiatives have been undertaken at the provincial level to streamline the ethical review processes and strengthen their respective clinical trial sectors.[22]

Several reviews and reports, including the Strategy on Patient-Oriented Research External Advisory Committee on Streamlining of Health Research Ethics Review (SHRER) 2013 [23] and the 2012 Action Plan [24] put forward recommendations to improve multi-site ethics review, with little effect. Similarly, efforts to establish a national program for the assessment of human research have stalled. The CCTCC Research Ethics Board Accreditation Working Group was formed in 2015 to review and assess the current situation regarding research ethics boards and to identify strategies to improve efficiencies using a system of REB accreditation. [25] In 2017, a review into the effectiveness of the CCTCC identified:

- Provinces continued to work in silos
- Duplication of work and lower patient engagement due to a lack of awareness and insufficient communication of CCTCC initiatives
- Inconsistencies and a lack of standardisation associated with the research approval processes remained
- Differing privacy regulations between provinces remained
- Costs associated with undertaking clinical trials continued to rise
- The need for greater harmonisation of regulations across provinces remained.

The review identified that the main reasons for the failure of previous efforts were the lack of leadership and clear authority to either undertake the required consultative work, or to provide the practical support necessary for implementing a proposed governance model. In the absence of national leadership in Canada, many provinces had implemented their own strategies to streamline ethics review, which has resulted in a diversity of harmonisation and streamlining processes.[26] Additionally, legislation varied between provinces (particularly in relation to provincial privacy legislation) and there remained concerns over the lack of equivalence in institutional liability and other administrative and risk-management issues.

Following a review of the CCTCC in 2017, a recommendation was made for establishment of a national strategic leadership forum to champion, shape and direct the development of organised research ethics at a pan-Canadian level, based on the rationale that a national strategic leadership forum might have a greater chance of success in Canada, given its federalist structure and the fundamental constitutional divisions affecting research ethics leadership in Canada.

# South Korea (The Republic of South Korea)

The South Korean Department of Health development has established the centralised South Korea National Enterprise for Clinical Trials (KoNECT) to foster and drive clinical research that is underpinned by policy and government fiscal support.

The clinical trial governance and regulatory system in South Korea is a highly organised centralised structure. There are two government departments that oversee and regulate clinical trials and pharmaceuticals: the Ministry of Health and Welfare and the Ministry of Food and Drug Safety. Other relevant agencies associated with clinical trials and involved with the sector's funding, development and governance include:

- The South Korea Health Industry Development Institute
- The South Korea Drug Development Fund
- The South Korean Association of Institutional Review Boards
- The South Korea Research Based Pharmaceutical Industry Association
- The South Korea Pharmaceutical Manufacturers Association.

The government has established a coordinated system of clinical trial research infrastructure across South Korea to address many of the governance issues detrimentally affecting clinical trials in developed countries.<sup>6</sup> At the top of the hierarchical structure is the Global Centres of Excellence Program which is funded by the Ministry of Health and Welfare and supports five consortia, each with a focus on a specialised area such as complex clinical trials, biomedical technologies and studies in special populations for Phase I clinical trials.

There are currently 22 clinical trial centres across South Korea that are jointly government and hospital funded. Each clinical trial centre is affiliated with a university hospital. Clinical trial centres have been designed to provide worldclass facilities and infrastructure, oversight of quality control, staff management and development.<sup>7</sup> There are also approximately 170 clinical trial sites across the country which are inspected and accredited and certified by the South Korean Ministry of Food and Drug Safety. A streamlined clinical trial authorisation process enables parallel ethics committee review and regulatory review to ensure that the process (from submission of an application to trial approval) takes no longer than four weeks. There are common IRB review application forms and mutual recognition systems for ethics review processes. Site-specific assessment approval is not required.

The South Korea Health Industry Development Institute<sup>8</sup> (the Institute) is a government-funded institution established in 1999 to provide a suite of services under four domains of responsibility: policy development and information sharing; reinforcing the capability of the health industry; health and medical service technology research and development support; and government project experience. The Institute has also established six global business offices to facilitate the promotion and expansion of the South Korean health industry and establish networks with local government agencies.

Improvements to clinical trial infrastructure are supported by a national network of clinical trial sites and designated government departments and organisations with responsibility for overseeing, coordinating, regulating and supporting clinical trials and the pharmaceutical industry. These networks and organisations are further supported by a centralised healthcare system, and near-universal national health insurance.[27]

In summary, the oversight of clinical trial operations in South Korean clinical trials is centralised, highly structured and organised with clear lines of responsibility and accountability for funding and regulation. The South Korean national approach to clinical trials governance has the advantage of centralised government, only one Ministry of Health and Welfare and significant government and industry investment, which has enabled South Korea to establish an extensive and sophisticated infrastructure for conducting clinical trials. Some of the initiatives introduced by South Korea may be transferrable to the Australian environment, for example, a centralised, online, publicly accessible database of clinical trials, standardised forms and templates for ethics review, and compulsory Good Clinical Practice education for research staff.

## Australia

Australia has the objective of being a preferred destination for clinical trials. The Australian clinical trial stakeholder landscape is complex, and no single government or agency holds all the levers for change.

The Australian Government in collaboration with jurisdictions is leading a body of work through the Council of Australian Governments Health Council to improve the environment for clinical trials.

In March 2017, the Council of Australian Governments Health Council agreed to further strengthen Australia's clinical trial sector through a new revitalised agenda for reform, using stimulus from the Commonwealth's \$7 million *Encouraging more clinical trials in Australia* initiative to support jurisdictional redesign of clinical trial operations around coordination hubs. Priority action areas identified in the Council of Australian Governments Health Council revitalised clinical trials agenda include:

- Coordination units new models to centralise and coordinate trial management
- Networks and partnerships maximised collaboration with trial networks communities of expertise/practice and registries, with an emphasis on cross-jurisdictional and discipline cooperation
- Enhancement of data and knowledge systems

   fast-tracked agreed metrics collection and improved data linkage capability, and support for mutual acceptance of ethical review
- Research as essential health system business

   embedding research and clinical trials into core hospital governance arrangements, including the use of performance measures
- Embedding clinical trials in safety and quality approaches – including collaboration with the Australian Commission for Safety and Quality in Health Care to establish a governance framework to support research in public hospitals.

The cross jurisdictional Clinical Trials Project Reference Group (CTPRG) under the Council of Australian Governments Health Council is charged with progressing the revitalised clinical trials agenda. Its stated purpose is to identify and implement actions and system redesign that will enable a streamlined and consistent national approach to clinical trials within Australia with the intention of enhancing health outcomes and building Australia's ability to attract national and international clinical trials. A further significant deliverable to date has been agreement on metrics to provide governments with reliable national information on clinical trial activity, and to support and measure the effectiveness of activities designed to improve the environment for trials in Australia. When fully implemented across all jurisdictions, national data will be available for the first time across a set of key strategic and operational objectives to drive quality improvement within the sector and to position Australia as a preferred location for clinical trials.

## **Medical Research Future Fund**

In 2015 the Government established the \$20 billion Medical Research Future Fund (MRFF) to provide a sustainable source of funding for vital health and medical research over the medium to longer term. The MRFF acts as an endowment fund and will, from 2020-21 effectively double Australia's investment in health and medical research. To date, \$1.7 billion in MRFF investments have been announced including over \$260 million to support clinical trials. MRFF funding is additional, and complementary to, the work of the NHMRC.

The Department of Health, together with other government and non-government agencies including the National Health and Medical Research Council, the Therapeutic Goods Administration, the Independent Hospitals Pricing Authority, Medicines Australia, and state and territory agencies, has developed resources to incentivise the clinical trials sector.

These resources include:

- Standardised clinical trial-site contracts
- Standard costs structures of per-patient costs
- Standard requirements for clinical trial medical expertise
- Standard requirements for data quality
- Standard metrics by which to report performance for improved local-site governance approval and site start-up timeframes and patient recruitment
- A reporting portal for trial sites to monitor the timeliness of site-trial processes
- Processes to promote consistency in safety monitoring and reporting of clinical trials for improved transparency

- Mechanisms to support trial-staff training through learning modules including the development of a vocational education and accredited training course
- Jurisdictional support for clinical trial networks
- A website for trial sponsors to raise public awareness of clinical trials more broadly (www.australianclinicaltrials.gov.au).

At the state and territory level, innovative approaches to clinical trial governance are underway. The literature review highlighted initiatives being undertaken in NSW Health, Western Australia Health and Western Health in Victoria. Initiatives undertaken in other jurisdictions will be included in a complementary mapping exercise that is being undertaken as part of the Clinical Trials Governance Framework project.

## **NSW Ministry of Health**

The NSW public health system is the largest public health system in Australia, comprising 17 local health districts and specialty health networks, 228 hospitals and 114,000 FTE staff.

In 2011, the NSW Government established the Health and Medical Research Strategic Review to develop a 10-year plan. The plan identified NSW's strengths and advantages to support health and medical research and made recommendations on improving the way research resources are developed and managed, including encouraging research and innovation in health services, leadership in clinical trials, strengthening the research workforce, and improving NSW Health research administration and infrastructure. The Office for Health and Medical Research (OHMR) was established to implement this 10-year plan.

Initiatives undertaken by the OHMR include:

- NSW research hubs
- NSW Research Ethics and Governance Reform Framework and Action Plan
- Collection of Ethics and Governance Metrics linked to Chief Executive Service Agreements
- Research Ethics and Governance Information System
- Early Phase Clinical Trials Framework
- Medical Research Support Program.

## Western Health, Victoria

Western Health services approximately 800,000 residents of the western region of Melbourne, Victoria. It manages three acute public hospitals (Footscray, Sunshine and Williamstown), a day hospital at Sunbury, a transition care facility at Williamstown and a large drug and alcohol service at Footscray. Western Health has a strong philosophy of working with its local community to deliver excellence in patient care.

In 2015, Western Health established and embedded the *Research Roadmap 2015–2020* which is aligned with the *Western Health Organisational Strategic Plan 2015–2020* and articulates the strategic direction for research at Western Health. It also identifies several challenges facing research at Western Health and whole-of-organisation outcome measures to monitor research success. A series of activities and associated metrics have been developed to measure the effectiveness of those actions. These metrics also measure and monitor wholeof-organisation commitment to delivering research outcomes and timelines for delivery.

## Western Australia

Western Australia Health has implemented the Western Australian Health Research Governance Framework. The framework governs the scientific, ethical and governance review and approvals of clinical trials and oversees the conduct and monitoring of human research within the Western Australian public health organisation. The framework aims to ensure effective and consistent research activity across the Western Australia health system through single ethical review of multi-centre research, the introduction of research governance and single ethical review standard operating procedures and standard ethics and governance forms and agreements, and the implementation of the Research Governance Service which is a centralised information technology system for investigators, project members, sponsors, site administrators, human research ethics committees and research governance offices.

## Conclusion

This literature review provides insights into successful approaches to clinical trial governance at a national and bi-national level that are particularly relevant in the Australian context to ensure consistency across the public and private health sectors. Key elements to consider in developing a national approach include:

- A national strategy with oversight provided by a national agency
- National policy and legislation
- National infrastructure including a technology platform
- Infrastructure to support the national strategic approach at the local level (jurisdictional and trial site)
- Local-site accreditation and auditing
- Streamlined ethics and site governance office processes
- Standard cost structures
- Mandatory staff training
- The efficient use of electronic health data (to facilitate the completion of site surveys, and support participant screening and recruitment)
- Local-site capability-framework with clearly defined organisational roles and responsibilities
- Standard operating procedures
- Agreed measures for reporting performance
- Collaboration with networks.

The next section provides the background to the challenges currently facing the Australian clinical trials sector and the subsequent sections provide the literature review methodology and key findings.

# Section 2: Background

## Key messages

- There is a perception that Australia is less competitive than emerging markets on metrics of cost, timeliness of trial start-up, and the capacity to recruit the number of agreed trial participants
- It is now widely recognised by government, industry and researchers that if Australia is to remain internationally competitive and continue to be an attractive destination for commercial trial sponsors, then reform is necessary
- The development of a national Clinical Trials Governance Framework (the Governance Framework) is a key element of a Council of Australian Governments Health Council agenda to revitalise the environment for clinical trials in Australia. The Governance Framework will strengthen governance arrangements for clinical trials, and provide clarity to governments, health services, hospital administrators, clinicians and others responsible for delivering clinical trials. An important aim is to reduce duplication and increase efficiency, cohesion and productivity across the clinical trials sector
- The Australian Commission on Safety and Quality in Health Care (the Commission) has been engaged by the Australian Government Department of Health on behalf of the jurisdictions to deliver the Governance Framework by mid-2019.The project stems from recognition by all health ministers that, while jurisdictions have worked to improve the environment for clinical trials, issues of fragmentation and inefficiency remain that affect Australia's attractiveness as a preferred location for clinical trials. The Clinical Trials Project Reference Group (CTPRG) is the expert advisory sub-group within the Clinical Principal Committee under the Australian Health Ministers' Advisory Council (AHMAC) tasked with progressing the Council of Australian Governments Health Council revitalised clinical trials agenda.

Clinical trial research is the link between science and clinical practice, and is provided at the interface between academia and industry.[28] Clinical trials are integral to the generation of evidence on the safe and effective development of therapeutic interventions and devices, and on the refinement of existing treatments to inform evidence-based practice. In the longer term they provide treatments to cure or manage disease, improve quality of life and prevent disability. [29] Additionally, clinical trials provide a range of benefits including commercial investment in the Australian research and development economy [30,31,32], and the creation of jobs in universities and research institutes, which attract and help retain world-class researchers and clinicians in the Australian healthcare system.

Investment in clinical trials is globally competitive and Australia needs to compare favourably with other countries to attract commercial sponsors. Australia has a reputation for excellence in clinical trial research, internationally recognised researchers and medical experts, quality infrastructure and high standards of health care.[30,32,33] This places Australia in a strong competitive position for the conduct of commercially sponsored clinical trials of complex design (such as, Bayesian adaptive trial design) and in complex therapeutic areas (such as, oncology).[30] Australia is considered a leader in the Asia-Pacific region for medical research and compares favourably with other clinical trial markets in countries with advanced health systems such as those in Europe and North America.

In 2016, over 6,000 Australians were employed in the clinical trials sector, working across approximately 1,000 concurrent clinical trials, either actively recruiting new trial participants, maintaining participants on trial treatments and/ or following patients after the receipt of trial treatment. Between 350 and 500 of these clinical trials are commercially sponsored and at least one-third of these are conducted on a global scale. Clinical trials are costly, approximating \$1.1 billion of investment in the Australian research and development economy. This total investment reflects roughly \$930 million from commercial trial sponsors and \$100 million from Commonwealth agencies and other funding sources, including clinical trial networks and medical research institutes (approximately \$64 million). Additionally, the Medical Research Future Fund will effectively double the Australian Government Investment in Clinical Trials. The Australian Government also provides tax incentives for commercial trial sponsors, and clinical trials provide cost savings to the Australian taxpayer through the Pharmaceutical Benefits Scheme (PBS) of around \$100 million per year for patient access to new therapies via clinical trials.[30]

## Clinical trials in Australia

Clinical trials are universally conducted within a strong regulatory framework determined by the International Conference on Harmonisation and Good Clinical Practice.<sup>9</sup> In Australia, clinical trial protocols are reviewed by a human research ethics committee (HREC) which is constituted according to guidelines issued by the National Statement on Ethical Conduct in Human Research (2007; updated in May 2015) by the National Health and Medical Research Council.<sup>10</sup> Informed participant consent is required and the HREC ensures all the possible benefits and risks of trial participation are disclosed to potential participants, and that the process for obtaining consent is properly undertaken. Additionally, local governance office review is undertaken at each trial site to confirm the capability of the site to conduct the trial.

The Therapeutic Goods Administration (TGA) provides a legislated regulatory framework for the availability of medicines, medical devices and biologicals within Australia. There are two TGA schemes under which clinical trials involving unapproved therapeutic goods may be conducted, the CTN Scheme and the CTX Scheme. The CTN scheme enables drugs and devices not registered on the Australian Register of Therapeutic Goods (ARTG) to be used in clinical trials, following notification to the TGA. The TGA's CTN scheme is often recognised as one of the fastest and most efficient regulatory processes for clinical trials globally.

There are also jurisdictional policies and procedures to guide the clinical trial process. The responsibility for undertaking this activity rests predominantly with local-site investigators (in hospitals) who work mostly within small teams with varying capabilities, organisational support and oversight. Given the complexity of the local Australian environment, there are multiple financial, clinical and administrative capability implications to be considered in the development of a governance framework for clinical trials.<sup>11</sup>

# Declining rates of clinical trial registrations in Australia

Australia experienced steady growth in the number of new clinical trial registrations with the TGA from 1998 to 2007. In 1998, there were 705 new clinical trial notifications through the CTN scheme.<sup>12</sup> This number increased in 2007, when there were 865 new clinical trial notifications. Thereafter, the number of new trial notifications declined and then plateaued. For example, in 2010 there were 574 new clinical trial notifications and in 2015 there were 469 new notifications. Between July and December 2016 there were 417 new trial notifications. Similarly, while the Australian New Zealand Clinical Trial Registry (ANZCTR)<sup>13</sup> reported moderate growth in the registration of non-industry-sponsored smallscale clinical trials, they reported no increase in the registration of commercially sponsored clinical trials from 2006 to 2015.

# Limitations of Australia as a preferred location for clinical trials

The reasons for the perceived decline in the number of new clinical trials are multifaceted. Australia has a small, geographically dispersed population. There are fewer patients per trial site and therefore a higher number of trial sites are required to recruit the same number of patients compared with emerging markets. Australia's capacity to recruit patients to clinical trials in some therapeutic areas is limited due to competing ongoing trials, limited avenues for clinicians to refer patients to a clinical trial and poor volunteer rates.

Australia is more expensive for Phase II and Phase III trials than markets in Asia and Eastern Europe and, overall, is less competitive in cost and efficiency. Commercial trial sponsors have reported up to 845% cost variation between separate Australian trial sites for the same activity on the same trial.<sup>14</sup> These factors affect the ability of local affiliates of commercial trial sponsors in Australia to compete for new trials with local affiliates of the same company elsewhere in the world on metrics of cost, timeliness of trial start-up, capacity to recruit to target and the quality of the trial data.

Australia competes predominantly for new trials with India, China, Brazil and emerging markets in Eastern Europe. These markets have the benefits of large patient populations, reduced costs, and systems to ensure quality trial data. However, it is not clear why Australia is not competitive with other developed nations that have higher costs for clinical trials such as the USA and Japan; countries with slightly lower costs such as Canada and the UK,<sup>15</sup> and countries with similar costs such as South Korea. In order to understand Australia's lack of competitiveness, government and non-government agencies have undertaken broad consultation with the clinical trials sector over the last five years which has revealed ongoing constraints to the efficient and effective conduct of clinical trials nationally.

Given the significant contribution that clinical trials (particularly industry-sponsored trials) make to patients, healthcare systems and economies worldwide, competition between countries to secure clinical trials is intense. Over the last decade a number of countries (including Canada, Singapore, South Korea, New Zealand, UK, India and USA) have recognised the value and importance of clinical trials and have implemented a range of initiatives to remain competitive – with particular focus on improving the operational and regulatory environment such as streamlining the process for gaining ethics and governance approvals.[8,34–36]

In Australia, a number of reports have highlighted the barriers to conducting clinical trials including long-standing variation between health services and jurisdictions, difficulties with patient recruitment, and lengthy start-up times due to duplication and inconsistency in ethics and governance approval processes. [30,31,33,37-39] In response, several initiatives have been undertaken including the National Approach to Single Ethical Review of Multi-Centre Research, which is designed to facilitate and enable single ethics and scientific review of multi-centre human research within and across Australian jurisdictions [40]; the National Mutual Acceptance Scheme<sup>16</sup>, and the development of a table of standard costs for conducting clinical trials in Australia.[41]

In summary, Australia is less competitive than emerging markets on metrics of cost, timeliness of trial start-up, and the capacity to recruit the number of agreed trial participants. It is now widely recognised by government, industry and researchers that if Australia is to remain internationally competitive and continue to be an attractive destination for commercial trial sponsors, then reform is necessary.

# **Project context**

Australia has the objective of being a preferred destination for clinical trials. In recognition of the important role that state and territory jurisdictions and hospitals have in progressing change in the clinical trials sector in Australia, the Clinical Trials Jurisdictional Working Group (now known as the Clinical Trials Project Reference Group) was formed in 2014 to identify and implement actions to enable a consistent national approach to multi-jurisdictional clinical trials within Australia, with the intention of enhancing Australia's ability to attract national and international clinical trials.

In April 2016, Council of Australian Governments Health Council noted that, although jurisdictions have worked to improve the environment for clinical trials, fragmentation and inefficiencies affect Australia's attractiveness as a preferred location for trials.

The Australian Health Ministers' Advisory Council (AHMAC) was tasked to develop options of best-practice models for organising sites and improving efficiencies, for better engaging sponsors and improving trial start-up times. The full AHMAC response, developed on its behalf by the CTPRG (including a recommendation for a national clinical trials governance framework), was endorsed by Health Ministers in 2017.

The CTPRG has now been charged with progressing the Council of Australian Governments Health Council revitalised clinical trials agenda. Its stated purpose is to identify and implement actions and system redesign that will enable a streamlined and consistent national approach to clinical trials within Australia with the intention of enhancing health outcomes and building Australia's ability to attract national and international clinical trials. The Commission has been engaged by the Department to undertake a project to develop the National Clinical Trials Governance Framework (the Governance Framework) as a first step towards nationally consistent accreditation of health services to undertake clinical trials. The key project deliverables include a literature review and mapping exercise which will inform the development of the Governance Framework and high-level implementation strategy. The Governance Framework will be underpinned by best-practice principles that are consistent with existing national standards and regulations for the conduct of clinical trials in Australia.

# **Section 3: Literature review**

# Key messages

- A review of the academic and grey literature was undertaken to provide evidence on governance frameworks for clinical trials in Australia and internationally, with an in-depth focus on national approaches to clinical trial governance in the United Kingdom, Canada and South Korea
- The search strategy encompassed English language reports from 2007 to the present of both the peer-reviewed literature and grey literature, comprising reports on clinical trials governance as well as policy documents and high-level reviews of governance frameworks in published and unpublished reports, policy documents and relevant materials obtained from a variety of sources, including websites of government and non-government departments
- The peer-reviewed literature identified system-level barriers affecting the conduct of clinical trials and the grey literature revealed processes undertaken by several countries to improve their local clinical trial environments including:
  - the establishment of an independent body or organisation to oversee, regulate and streamline disparate arrangements for ethical approval and the provision of a new national research governance service
  - carefully constructed and judiciously governed national accreditation systems to assess local-level providers to confirm they have implemented the nationally harmonised approach to clinical trials governance

- the integration of research into routine healthcare to foster a research culture in health organisations, and encouragement for health administrators to invest in the research activities of their institutions
- the provision of incentives, through funding agreements for health services to engage in research support and measures of clinical research key performance for health service administrators
- mandatory staff education and project monitoring throughout the course of a trial to improve clinical research practice
- consistency across jurisdictions in relation to ethical and local-site approval for a single rigorous review by a reputable national group accepted by all hospitals (public and private) and regulators
- clearly articulated performance metrics for domains within an accreditation standard that consider all aspects of governance including infrastructure, human resources, financial management, site management, study management, data management, continuous quality improvement and protection of research participants
- mandatory requirement for all clinical trials to be registered on a publicly available website with publicly available summary results and information on trial outcomes.

A review of the academic and grey literature was undertaken to provide information on governance frameworks for clinical trials in Australia and internationally, and to provide focused insights into the governance of clinical trials from three developed countries. The search strategy encompassed both the peerreviewed literature (published articles in peerreviewed journals) and grey literature comprising reports on clinical trials governance as well as policy documents and high-level reviews of governance (published and unpublished reports, policy documents and relevant materials obtained from a variety of sources, including websites of government and non-government departments).

The search strategy focused on English language reports from 2007 to the present. The following were considered for inclusion:

- Literature considered relevant to the governance of clinical trials in hospitals
- Reviews or evaluations of frameworks of clinical trials governance
- Issues pertaining to the conduct of clinical trials in hospitals
- Discussion papers on the conduct of clinical trials.

A narrative review method was used to present a broad perspective on clinical trials governance with reference to historical issues, and approaches to addressing these issues in current clinical trials governance frameworks. A narrative approach recognises that not all research designs are comparable and enables presentation of national and international perspectives of patients and consumers, governments, hospital administrators, health services that deliver clinical trials, private companies, trial sponsors and trial investigators. The narrative method requires the critical appraisal of each source to identify those sources eligible for inclusion in the review. An overview of the process for undertaking the narrative review of the literature is provided in Table 1.

A general review of the topic area was conducted prior to keywords being identified. The key search question and the sub-questions were subsequently developed. An Endnote database was established to organise and store the journal articles and the grey literature, and to manage references and citations.

## Key question

What mechanisms exist, or are recommended, for clinical trials governance at the hospital level, and/or funding health agency level in Australia and internationally?

### **Sub-questions**

What clinical trials governance mechanisms exist, or are recommended?

What are the key components of these mechanisms?

What are the stated rationales for the use of these mechanisms?

What are the barriers and facilitators to implementing the identified mechanisms?

What evidence is there for the impact of these mechanisms?

Task	Step
1	The scope of the review is determined by the contract <sup>17</sup>
2	Research questions are developed based on:
	<ul> <li>The specific topic of interest</li> </ul>
	<ul> <li>Rationale for the review</li> </ul>
	<ul> <li>Timeframe for the search</li> </ul>
	<ul> <li>Target audience</li> </ul>
	<ul> <li>Practical limitations to the search.</li> </ul>
	Search focus: healthcare settings in Australia and internationally.
3	A general review was conducted, to determine key concepts and keywords.
4	Key journals were then identified for potential hand-searching of the literature.
5	The type of review and the type of literature was then considered. That is, either conceptual (narrative) or systematic review and the type of literature, either grey and/or peer-reviewed. The types of articles were also considered and the rationale for including commentary, opinions and letters.
6	Overarching questions and sub-questions were then drafted.
7	Search terms were derived from step 6 – according to the database(s) to be searched and MeSH terms, keywords, explode or focus applied. For each key concept in the question, synonyms and related concepts were searched.
8	Draft search strategy was developed using Boolean logic, inclusion and exclusion criteria, and limiters.
9	A record of each decision made to include articles was developed and the rationale for its use was stratified using the PRISMA flowchart.
10	The draft search strategy was then tested with one database.
11	The search question was then refined to further refine the inclusion and exclusion criteria and scope of the search.
12	The Endnote database was established.
13	The finalised search strategy for each database was then conducted.
14	The findings were imported into Endnote and duplicates were removed (automatically and manually).
15	All titles were screened according to the search criteria and obvious exclusions were removed.
16	Relevant abstracts were screened, obvious exclusions were removed and a shortlist of other closely relevant titles was created.
17	Full-text articles were obtained and read (PDFs were imported and annotated in Endnote). Obvious exclusions were removed and summaries of the remaining articles were developed.
18	A manageable amount of articles were determined. This amount was limited a maximum of approximately 100.
19	Articles were divided into themes manually, based on the questions developed and the purpose of the review.
20	A summary of findings was developed by themes.
21	The themes were then integrated into the final discussion section and recommendations were made based on the weight of the evidence, and its implications for this project.
	1         2         3         4         5         6         7         8         9         10         11         12         13         14         15         16         17         18         19         20         21

<b>Table 1:</b> Process for undertaking the narrative review of the	literature
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# Search strategy of the peer-reviewed literature

The search strategy of the peer-reviewed literature comprised a range of study designs including: randomised controlled trials, controlled clinical studies, quasi-experimental designs, descriptive studies of programs, pilot studies, conference papers, reviews and commentaries. All titles, abstracts and, where available, full-text articles were retrieved for this review. The reference lists were hand-searched to ensure the review was comprehensive and if papers were found that had not previously been identified the titles and abstracts were then reviewed. If these additional papers or reports met the inclusion criteria of the search, they were also retrieved (Table 2).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used to stratify the peer-reviewed literature based on the inclusion criteria (Figure 1).

The following keywords were used in the search strategy: clinical trials; medical research; governance; governance framework, organisation and administration; hospitals; regulatory framework and health facilities. The search terms for the academic literature were determined after reviewing medical subject headings (MeSH) from the US National Library of Medicine and subject headings for CINAHL and the Health Policy Reference Centre.

The following databases were searched for peerreviewed literature:

- CINAHL
- Medline
- Health Policy Reference Centre
- BMC Proceedings (to search for proceedings of conferences including abstracts and full articles)
- Open Access Theses and Dissertations (to search for international theses) and Trove and Libraries Australia (to search for Australian theses)
- Centre for Reviews and Dissemination (University of York)
- Google Scholar
- Cochrane Library.

In addition, the following journals were handsearched:

- Clinical Trials
- Trials.

**Inclusion criteria Exclusion criteria** Published/available in English Unavailable in English Published between January 2007 and the Published prior to January 2007 present Human research Animal, in vitro Includes commentary on governance of clinical Does not include commentary on governance of trials at the hospital and/or funding health clinical trials at the hospital level and/or funding agency level health agency level Includes evaluation of governance frameworks Does not include evaluation of governance for clinical trials at the hospital and/or funding frameworks for clinical trials at the hospital and/ health agency level or funding health agency level

**Table 2**: Search eligibility of the peer-reviewed literature

# Results of the peerreviewed literature

The first stage of the review of the academic literature involved a scan of the search results from each electronic database by reading through the titles and abstracts. Potentially relevant articles were then downloaded into an Endnote database for further scrutiny. During this initial scan 513 articles were identified as being potentially relevant to the literature review. A further 21 articles were identified through snowballing from the reference lists of relevant articles, forward citation searching and author searches. Some articles were captured several times through various database searches requiring the removal of 109 duplicates. The total number of journal articles included in the Endnote database was 425. The abstracts of all the journal articles included in the Endnote database were read and assessed for suitability

against the eligibility criteria. A total of 189 records were excluded as they did not meet eligibility criteria and 236 full-text articles were further assessed for relevance against the research questions, with 170 records excluded on the basis that they were only marginally relevant. A total of 66 papers were included in the final review (Figure 1).

The peer-reviewed literature were predominantly: descriptive cohort studies; case studies; commentary and commissioned reports highlighting issues associated with an expanding globally competitive clinical trial market, cost burden and delays in the time taken to activate a clinical trial, organisational and administrative barriers to conducting clinical trials, and recommendations and activities undertaken to improve the clinical trial operating environment. There were no studies describing the implementation or evaluation of a governance framework for clinical trials at either the hospital level or health service funding level.

#### Figure 1: PRISMA flow chart for the peer-reviewed literature



# Discussion of findings from the peer-reviewed literature

Over the last decade the governance of clinical trials has been the subject of commentary and discussion largely focused on the issues associated with ethical review and local-site governance approval, which is universally seen as overly bureaucratic, inefficient, fragmented, costly and lengthy.[15,42,43] Paradoxically, despite commonly held concerns, evidence on how clinical trials can best be governed and regulated is limited to case studies, commentary and commissioned reports [17,44]: 'given the amount of commentary and the reported waste and inefficiency in the regulation and management of research worldwide the paucity of qualitative and quantitative research documenting and investigating solutions to it is surprising'.[36]

Several cohort studies reviewed clinical trial regulation in a single country or compared research regulation between countries. In Finland, a qualitative review of factors contributing to the fragmentation of clinical trial operations and resourcing was undertaken. The participants included stakeholders from government departments, industry, academic institutions, health services and researchers. A review of clinical research policies, funding sources and the volume of research activity was also undertaken. The study findings indicated that - in the absence of national policy or an overarching organisation to guide and coordinate clinical research across health and health research agencies, combined with a passive health ministry, clinical trials in Finland were largely driven by researchers. The researchers attributed fragmentation to the decentralised structure of health services and health policy, and proposed the establishment of a coordinating institution with responsibility for monitoring research activity.[45]

In the European Union, comparisons of medical research regulations found differences in the application of legislation across member nations. The number of research ethics committees in a single country varied from one to 264; and there were no standard practices informing their roles and responsibilities, working principles or timeframes for clinical trial approval. Additionally, there were few avenues to appeal a negative decision by an ethics committee in 10 European countries. In five European countries the ethics committee was not accountable to any organisation and processes such as obtaining participant informed consent varied widely between research institutes.[46]

The World Health Organization Western Health Regional Office for the Western Pacific Expert Committee's review into improving health research management and governance in the Western Pacific [47] found the ethical and governance review process articulated the broad goals of health research management and governance in the region - namely, accountability, transparency and efficiency in health research. Six essential health research governance and management roles undertook the functions of monitoring overall research activity at the national level, including identifying and pursuing national priorities in health research; building, strengthening and sustaining national health research capacity; creating systems to facilitate wider access to clinical trials; and the dissemination of trial findings.

Each essential health research and management function was reviewed according to three criteria:

- 1. The relevance of the function to improving accountability, efficiency and transparency
- 2. Current status and barriers preventing the performance of the function
- 3. How the function might be performed by national organisations.

Actions arising from the World Health Organization review included the creation of appropriate bodies in each member state with responsibility for policy development and strategic planning for clinical trials, and oversight of the human and financial resources required to fulfil these functions. Other recommendations included the creation of national health research registries, access to research data, and development of ethical standards in line with international standards and guidelines.[47]

Organisational and administrative barriers are the factors most frequently identified in the literature as impeding the conduct of clinical trials. Several countries, including Australia, the United Kingdom (UK) and the United States of America (USA), observed that ethical and governance review of clinical trials is overly complex, inefficient, time-consuming and costly. [3,5,17,8,10,12,16,34,36,48–60]

Delays in the activation of clinical trials due to discordant functions, duplication and inefficiency noted in the peer-reviewed literature are magnified when conducting multinational clinical trials.[61,62] These delays are due, in part, to differences in national regulatory and ethics requirements or governance review processes applied by one country to another. [5] Multinational collaboration on clinical trials has increased considerably during recent years but significant barriers remain relating to trial complexity and timely review, and costs associated with conducting clinical trials.[5]

A review of the literature to identify the costs of institutional review board reviews in the USA derived costs from 52 studies to demonstrate that review boards operate at different levels of efficiency and that there is a time burden associated with review board review. Although there was insufficient evidence for valid estimates of the magnitude of the effects, the authors highlighted the need for a single, central IRB review for multi-centre studies, and a mechanism to systematically track the interaction between researchers, sponsors and IRB review offices.[42]

In Australia the costs, complexity and time delays associated with clinical trials are compounded by inter-jurisdictional and regulatory differences between private and public sites, resulting in the need for repeated institutional governance reviews and separate regulatory approvals, which may have to be sought consecutively rather than simultaneously.[63] In the absence of centralised regulatory approval, multicentre clinical research can require as many individualised applications for regulatory approval as there are institutions participating in the study.[36] Duplication and variation in the documentation to support a clinical trial submission persist, despite efforts to streamline and harmonise the ethical review process.[11]

Several observational studies have quantified the impact of decentralised ethics and governance approvals on staff time, study costs and delays in study commencement.[53,55,56] The costs of two large Australian multi-centre studies were compared for obtaining ethical and site-specific approvals. The cost of staff time to obtain trial approval was expressed as a percentage of the total trial budget. The total costs of gaining approval for 50 clinical trial sites comprised 38% of the budget (mean cost \$6,960 per site) and a large proportion of staff time (75–90%) was spent on repeated and time-consuming tasks such as reformatting documents, which did not improve the study design or participant safety.[43]

A prospective descriptive study undertaken by White et al. between 2012 and 2015 investigated the time and documentation required to gain ethics and governance approvals for a multi-centre study being conducted in several Australian states, both with and without a centralised ethical review system. The main outcomes measured were time to approval (in weeks) for ethics and governance, and the number and type of documents submitted. A centralised ethics-approval process was used in five states, with approval taking between 2 and 18 weeks. One state did not use a centralised process, with ethics approval taking a median of 4.5 weeks (range: 0–15) per site. In four states using a centralised ethics process, 33 governance applications were submitted, with 20 of these requiring a site clinician listed as an investigator.

Governance applications required the submission of 11 documents on average, including a site-specific assessment form. In total, 32 governance applications required original signatures from a median of 3.5 (range: 1–10) non-research persons, which took a median of 5 weeks (range: 0-15) to obtain. Governance approval took a median of 6 weeks (range: 1-45). Twelve research study agreements were needed, each taking a median of 7.5 weeks (range: 1-20) to finalise. The authors concluded that the benefits of centralised ethics review systems have not been realised due to duplicated, inflexible governance processes. A system that allowed the recognition of prior ethical approval was more efficient than central ethics and sitespecific governance approval.[57]

Similarly, Vajdic et al. investigated the time taken for governance approval of multi-centre studies through the site-specific approval process. These authors found that the median total governance approval time for 28 submissions was 12 weeks (range 2.5-64 weeks), the median time from starting the site-specific assessment to submission was 8 weeks (range 1-48) and the median time to governance approval was 5 weeks (range 0.3-40). Approval times were shorter for public compared with private institutions. Reasons for delays in finalising submissions for approval were the absence of institutional governance officers, lack of clarity regarding signatories, the need to identify a principal investigator employed by the institution and the lack of recognition of ethical approval by private institutions. The need to develop legal agreements between the university and hospital was the main reason for lengthy delays in obtaining approval. The authors concluded that the advantages of a harmonised single ethical review process were undermined by the coexistence of a fragmented, complex and lengthy governance approval process.[64]

In the EU, Clinical Trials Directive EU 2001/20/EC<sup>18</sup> was viewed as an important step to simplifying and harmonising the administrative provisions governing clinical trials across EU member states and to sustain innovation and competitiveness in clinical trials.[65]

The anticipated benefits of the directive failed to be realised however due to differences in the way the directive was implemented within each country's legislative framework. [66,50,5,65,48,67–69] As argued by Van Oijen: 'If legislation intended to strengthen harmonisation is not carefully implemented, it can become counterproductive to its aims'.[2]

The impact on patient health outcomes and access to new therapies, due to lengthy approval processes and inconsistencies related to decentralised ethics approvals, has also been examined. A study by Christie et al. [70] extrapolated the delay in ethics committee approval for multi-centre clinical trials of cancer treatment (and the subsequent delay in obtaining trial results) on survival of patients with cancer in Australia. The authors estimated these delays equated to 60 cancer deaths per year and coined a term to describe the accrual curve: DIABOLECAL (Delays in accrual brought on largely by ethics committee activity lag-time). In 2011 a model was developed to estimate the deaths caused by research delays. This considered factors associated with ethics review committee review and approval times, and the differential utilisation of research results.[71]

In summary, the system-level barriers identified in the peer-reviewed literature as affecting the conduct of clinical trials included:

- Lack of a universally agreed set of good governance principles [48]
- Lack of monitoring and reporting on ethics and governance processes to track and compare the operational performance of research coordination offices and research governance offices. This affects the ability of researchers to track their application and identify the cause of delays [3]
- A lack of research infrastructure to facilitate the development and management of clinical trials. For example, specialised clinical research centres and academic clinical trial units organised into larger networks with services for the preparation, design and conduct of clinical trials for any disease area [5]

- Limited clinical trial productivity due to the absence of an agreed framework for clinical trial-site standards [16] which would underpin voluntary clinical trial-site accreditation [16]
- Underuse of technology to improve clinical research capacity, such as the electronic health record [10], online or electronic ethics and governance application forms [48], secondary-use research data [72], datalinkage techniques to obtain health outcomes data [10] and fragmented electronic patientdata systems [34]
- A lack of standard operating procedures, forms, templates [17]
- Difficulty meeting recruitment targets [73–78] and retaining clinical trial participants [79]
- Few incentives for clinicians to be involved in international clinical trials [34,80,51]
- Clinical research is not viewed by health organisations as 'part of the mission'.[34] Prior to the implementation of the current research framework in the UK, it was noted that the National Health Service (NHS) trusts (hospital networks) failed to see the link between health service delivery, research, improved patient outcomes, good service development and staff retention.[12] Moreover, although some NHS trusts foster research, other trusts regard research as an indirect activity or as an income stream. This perspective is echoed in the 'inefficient and bureaucratic behaviour' present in the Australian health system and the prevailing view of research being an 'encumbrance' for hospitals [11]
- No requirement or incentive for hospital boards and chief executive officers to ensure that systems for research are in place and working [12]
- No central registry for researchers [17]

   unnecessary honorary appointments, contracts, letters of access and criminal record checks for researchers and duplication of jurisdictions' requests for these checks [17]
- Lack of awareness and understanding by clinical researchers of good clinical research practice and the roles and responsibilities of researchers, institutions and research ethics committees [5]
- Clinical trial/research regulation is not proportionate to risk – that is, the extent to which patient safety is likely to be jeopardised. There is no assessment of the balance of risk and regulation or guidance on what constitutes a low-risk clinical trial,

to reduce the heterogeneity of review by ethics committees and research governance offices [3,17,13,48]

- Late registration of clinical trials [6]
- Poor performance and variation in the sharing, reporting, dissemination and publication of clinical trial results [81–84]
- Fractionally implemented policies and legislation.[2]

# Search strategy of the grey literature

A purposive search strategy of the grey literature provided published and unpublished reports, policy documents and relevant materials obtained from a variety of sources, including websites of government departments and private companies (Table 3).

The grey literature search comprised a review of policy documents and reports of clinical trials governance processes from Australia, New Zealand (NZ), the UK, the USA, Canada, the Nordic region, South Korea and several European countries. A review of the international grey literature enabled comparisons of guiding policies and clinical trial governance frameworks (either implemented or proposed) and the evaluation of the frameworks in countries with similar systems of government and health service provision as Australia. Additionally, a search of Google and Google Scholar was also conducted. After the general review of the grey literature was conducted, three countries (where a national approach to the governance of clinical trials had been implemented) were selected as a focus for this review: UK, Canada and South Korea.

The following grey literature databases were searched:

- MedNar
- CORE
- APO Australia
- BASE
- WorldCat.

Table 3: Search eligibility criteria of the grey literature

Inclusion criteria	Exclusion criteria
Published/available in English	Unavailable in English
Published between January 2007 and January 2018	Published prior to January 2007
Human research	Animal, in vitro
Included details of recommendations, mechanisms, procedures, regulations, standards, policies, frameworks for the governance, oversight or managing of clinical trials at the level of hospitals or higher	Does not included details of recommendations, procedures, regulations, standards, policies, frameworks for the governance, oversight or managing of clinical trials at the level of hospitals or higher

To find publicly reported information a search of websites belonging to the following organisations was conducted: the National Health Service (NHS), National Institute for Health Research National Institutes of Health (NIH), Canadian Institutes of Health Research, The King's Fund; South Korean Ministry of Health and Welfare; New Zealand Ministry of Health; Commonwealth Department and state and territory departments of health; and the National Health and Medical Research Council. The websites of the World Health Organization (WHO); Welcome Trust/Collection UK; New York Academy of Medicine; National Academies Press were also searched and an advanced Google search was undertaken using the truncated phrases of keywords including:

"clinical trials\*" AND governance

"clinical trials\*" AND organisation AND administration

"clinical trials\*" AND hospital AND governance

"clinical trials\*" AND governance AND framework

"clinical trials\*" AND governance AND regulatory AND framework

"clinical trials\*" AND governance AND regulatory AND health facility

"medical research\*" AND management AND hospitals

# Results of the grey literature review

More than 385 records were located through the grey literature search. Of these, 76 records were included in the literature review (based on the inclusion and exclusion criteria). In addition, information from 70 websites was extracted and included in this literature review. A summary of the grey literature included in this review by country is provided in Table 4.

**Table 4**: Results of the grey literature by country

Country	Number of records	
Australia	25	
New Zealand	7	
United Kingdom (UK)	18	
United States of America (USA)	7	
Europe	3	
Canada	7	
South Korea	9	

The grey literature search revealed that, in the first two decades of the 21st century, a number of countries, including Australia, Canada, New Zealand, the UK, the USA and some European countries, either commissioned or conducted high-level reviews of their respective clinical trial and medical research sectors. The reviews were initiated in response to commonly held concerns including increasing global clinical trial competitiveness, the declining market share of clinical trials, and evidence that respective local regulatory and governance systems had contributed to trial start-up delays, increased costs and low patient-recruitment. These reviews identified the barriers and challenges associated with conducting clinical trials and suggested strategies to improve efficiency while continuing to maintain high-quality clinical trial standards and protect patient safety.

While the discourse was similar across countries the solutions varied.[85] For example, Australia, Canada and the UK have single-payer systems that facilitate centralised research management whereas the USA health system is fragmented and predominantly a fee-for-service, user-pay model which impedes the implementation of a national approach. The literature suggested that any systemic change adopted by a country (such as a clinical trial governance framework) will, to a large extent, be determined by prevailing government policies and the motivation and priorities of decision-makers. Similarly, the sociocultural and economic environment also shaped solutions.

## New Zealand

In February 2010, the New Zealand Health Select Committee opened an inquiry into the clinical trial operating environment. The health committee had initiated the inquiry based on concerns that 'New Zealand had lost its advantage as a good place to carry out clinical trials'. The terms of reference for the inquiry were to consider:

- A coordinated nationwide approach to clinical trials and performance measures
- Streamlined ethics-approval systems
- National patient-referral networks, and better ways to approve, establish and conduct clinical trials

- The removal of unnecessary barriers to the conduct of clinical trials
- Benefits to New Zealand patients, as well as the New Zealand innovation system, health system and economy through clinical trials.

In June 2011, the health committee handed down the findings of the *Inquiry into improving New Zealand's environment to support innovation through clinical trials*.

The inquiry identified several factors impeding the development of a more productive clinical trial environment and made a number of recommendations to the government on how these recommendations could best be implemented.[86]

### **Historical perspective**

### Ineffective regulatory framework

The existing regulatory framework was identified as being robust but slow due to administrative inefficiencies in the ethical review process and the operation of the health and disability ethics committees (HDEC). The mean time taken for clinical trial approval was identified as being considerably longer than in other countries and had reduced New Zealand's attractiveness as a site for commercially sponsored multinational clinical trials. Several factors were identified as affecting the clinical trial ethics review process including:

- Variability in decision-making by ethics committees
- Duplication in the processes carried out by HDECs and district health boards in locality assessments
- Paper-based application process (rather than electronic and online)
- Ethics application processing fees
- The size, composition and resourcing of ethics committees.

International benchmarking, harmonisation of internal review processes and alignment with the regulatory review systems in other countries, were highlighted as options to developing a more robust, efficient and streamlined approval process in New Zealand.

#### The role of Pharmac

Pharmac is the New Zealand Government body responsible for managing the Pharmaceutical Schedule which lists government-subsidised medicines. Recommendations from the review were made to establish innovative mechanisms to build constructive, transparent and professional relationships between government and the international pharmaceutical and biotechnology industries, while not undermining Pharmac's role in purchasing pharmaceuticals.

#### The role of district health boards

The inquiry noted that one of the functions of district health boards (DHBs) was to carry out a 'locality assessment' of a proposed trial to ensure suitable arrangements and resources for the investigator to conduct a clinical trial. However, there were no standardised processes or documentation for the DHBs, which resulted in duplication, lengthy approval times, lack of standard clinical trial agreements and no agreed or transparent methodology for determining the costs charged to conduct a clinical trial. There was also variation in review charges and additional overhead charges imposed by DHBs as a percentage of the clinical trial revenue. The inquiry revealed there was a perceived failure of the DHB sector to promote its value as a source of innovation and new knowledge, which would justify investment in the equipment and infrastructure required to conduct clinical trials. This was reflected by the limited ability of DHBs to view clinical trial research as 'core business' or an essential part of hospital activity.

It was recommended that New Zealand develop a national health research action plan to foster innovation and commercialisation and a framework for clinical trial research to which DHB clinical trial responsibilities could be aligned. This would include explicit requirements for DHBs to be involved in clinical trials (including reporting requirements). Crown Funding Agreements between the Minister of Health and DHBs were also discussed.

Also raised for consideration was the need for government to provide DHBs with appropriate funding to enable them to undertake clinical trials as a front-line activity (including the purchasing of technology and infrastructure as well as supporting a clinical trial workforce) and the option of replacing individual DHB research offices with clinical research networks comprising multiple DHBs.

### Information technology

The inquiry raised issues relating to information technology planning which ranged from the need to improve the system for collecting national data on clinical trial activity (for example mandatory clinical trial registration on either a New Zealand or overseas clinical trial register) to the utilisation of health information technology for research, including the electronic patientrecord systems. Recommendations were to establish links to national clinical databases and develop a set of national metrics to monitor clinical trial activity.

### Funding clinical trials infrastructure

The inquiry noted the financial incentives established by the government (including tax credits and funding schemes) to support public and private research investment; however, the low levels of private and government investment in research and development in New Zealand relative to the OECD average could be linked to under performance. The inquiry recommended a coordinated government response and strategy to prioritise, support and foster research and innovation through increased public funding and the promotion of New Zealand as an environment in which to conduct clinical trials.

# Strategic planning for change in New Zealand

The inquiry made a total of 54 recommendations including to simplify and streamline ethical review processes, promote collaboration between government departments to coordinate the system, develop a national health research action plan to foster innovation and commercialisation and develop a framework for clinical trial research DHBs facilitated by a 'research hub'. Specifically, the recommendations were for:

- Development of a national strategy for clinical trials and research at DHBs that is endorsed by the Ministry of Health to ensure research is a core activity undertaken by DHBs and supported by a funding stream
- Purchasing research infrastructure to support clinical trials on a national platform so that as many institutions as possible can benefit from the investment
- Improving the availability of information by requiring clinical trials to be registered on the Australian New Zealand Clinical Trial Registry.

# Research and development and infrastructure support

- Establish a long-term objective for research and development investment in clinical trial infrastructure to run clinical trials
- Establish a medium-term objective of bringing New Zealand's public and private investment in research and development up to international benchmarks
- Establish mechanisms to promote New Zealand as an intelligent global player in the clinical trials sector.

# Collaboration between government and industry

- Build constructive and transparent relationships with the international biotechnology and pharmaceutical industry
- Consider models to facilitate the development of constructive, professional and transparent relationships between Pharmac, the pharmaceutical industry and the New Zealand Government.

# Streamlining the regulatory approval process for drug applications

- Develop a streamlined regulatory review process for drug applications which is more aligned with the Australian Clinical Trials Notification and Clinical Trials Exemption schemes
- Assess relevant, overseas clinical trial reports (Australia and UK) to inform future regulatory approval process development.

Recommendations were to:

- establish a national framework for clinical trial research to be implemented by DHBs
- allocate government funding for DHBs to undertake clinical research including funding to purchase technology
- use key performance indicators to monitor performance relating to timeliness and the cost and efficiency of carrying out clinical trials, such as, expedited reviews should be processed within 30 calendar days and other applications within 45 calendar days
- remove duplication in the ethical review process and adopt an aligned approach when implementing nationalised agreements with sponsors engaged in multi-site clinical trials
- establish the appropriate infrastructure to support clinical trials as well as encourage clinicians to undertake clinical research through incentives or funding.

#### Streamlining the ethical review process

- Review the number and composition of ethics committees and consider establishing a new, dedicated ethics committee for sponsored clinical research with an application fee charged on a cost-recovery basis
- Remove duplication in the processes carried out by ethics committees
- Develop standardised operating procedures for ethics committees to ensure consistency in decision-making within and between ethics committees, as well as standardisation of the processes and documentation required by DHBs
- Introduce a system of electronic submissions of clinical trial applications to improve the efficiency of ethics committees
- Assess the options for charging fees for ethics committee review
- Implement a simplified, optional standard clinical trial agreement for all applications.

In September 2011, the New Zealand Government issued a response to the report provided by the health committee following the inquiry. The government accepted the report and indicated that it would take action on many of the committee's recommendations. The government also announced changes to the health and disability ethics committee processes and noted these would improve New Zealand's clinical trials environment without additional expenditure and in a relatively short timeframe. To effect these decisions, procedural rules - called standard operating procedures - were developed for the health and disability ethics committees in collaboration with key stakeholders and following a public consultation process.[87] The standard operating procedures came into effect on 1 July 2012 and were subsequently revised in 2014.[88] The standard operating procedures outline the roles and responsibilities of health and disability ethics committees (HDECs) in New Zealand and the ethical review process, including the 35-day review clock which stipulates that within the full review pathway, HDECs must make a final decision within 35 calendar days.[88]

### New Zealand Health Research Strategy 2017–2027

One of the recommendations arising from the health committee's inquiry was to develop a national health research strategy or action plan. This recommendation was reiterated by the Health Research Council (HRC) in its 2015 review titled Strategic Refresh of the Health Research Council. Closely aligned with this was the HRC recommendation that health research be embedded into both the health sector and the wider innovation system, and that strategic alignment of, and connections between, stakeholders in the health research system be improved. The rationale behind this strategy was to ensure the pipeline for clinical trials operated more effectively from concept through to early and late phase clinical trials, and that research findings were disseminated. The HRC recommended that a health research strategy, when developed, would drive this change.[89]

In May 2016, the government published the New Zealand Health Research Strategy: Public discussion document. This was followed by the New Zealand Health Research Strategy 2017–2027: Summary of submissions and consultation, which provided analysis on submissions received and key themes emerging from public consultations and focus groups.[90] A recurring theme within the findings of these discussions was the need to establish a strong clinical trial industry in DHBs. Those providing feedback suggested the following actions to encourage DHBs to engage more fully in clinical trials:

- Clinical trials should be considered a key priority for district health boards and measurable using key performance indicators
- Clinical trials should be embedded as a separate function of DHBs within Section 23 (Functions of district health boards) of the New Zealand Public Health and Disability Act 2000. Section 48 of that Act embeds research as:
  - a function of Pharmac
  - investigator-led research and cooperative group trials should be a key priority for district health boards, accepting that they may continue to use paid commercial research to help fund them.

Public submissions highlighted the benefits for stakeholders in New Zealand to connect with international clinical trial sponsors and to develop national-level clinical trials networks and a national clinical trials body. It was envisaged that the national body would manage database development, information security, standard operating procedures, randomisation technologies, monitoring of trials to ensure appropriate conduct, data and statistical advisory services, standard (pro-forma) contracts and good clinical practice training, and monitor compliance with good practice and data and safety monitoring committees.

In 2017, the *New Zealand Health Research Strategy* 2017–2027 was published.[91] This document sets out a 10-year strategic plan for the health research system. The government's vision for health research by 2027 is for 'New Zealand to have a world-leading health research and innovation system that is founded on excellent research and improves the health and well-being of all New Zealanders'. Four principles (research excellence, transparency, partnership with Maori and collaboration for impact) guide all policy settings, investment decisions and operational procedures. The current research strategy articulates a framework for collaboration and contribution across the health research and innovation system including identifying specific roles and responsibilities. The implementation strategy identifies the Minister of Health and the Minister of Science and Innovation as having joint responsibility for overseeing the implementation of the strategy. Performance indicators to monitor and evaluate progress towards achieving the vision are also listed, although they are not mandated. Proposed metrics include:

- The number and types of health research undertaken, the number of clinical trials conducted in health service identified priority areas
- The time taken by ethics committees to approve research proposals
- The time taken to translate findings into policies and practices
- The number and types of research using New Zealand's health and social data infrastructure.



Figure 2: Overview of the New Zealand approach to clinical research governance

Another high-level report highlighted through the literature review pertaining to clinical trials in New Zealand was the *Research to Action: Improving the Lives of New Zealanders through Health Research: HRC Investment Impact Report for the Ministry of Business & Innovation & Employment* by the Health Research Council of New Zealand. [92] Published in 2015, this document served to outline how the HRC of New Zealand contributes across the full value-chain of health research, from 'generating the fundamental knowledge needed to germinate ideas right through to the clinical testing of innovations in our health system'.

The document notes the significant global investment in clinical trials and the potential return on investment in clinical trials. The key message arising is the need for the New Zealand Government to continue supporting, investing in, and strengthening the innovation value-chain of clinical research. The document notes this is best achieved through encouraging and incentivising research into converging technologies, exploring commercial potential and critical research capability, and providing targeted training to build New Zealand's clinical trial assessment and clinical trial monitoring expertise.

#### Note

The HRC is a Crown agent established under the Health Research Council Act 1990 (the Act). The HRCs overall purpose is to 'improve human health by promoting and funding research'.

The HRC is the agency responsible for managing the New Zealand Government's investment in health research and is the only funder supporting clinical trials of novel drugs and biologics in patients. The HRC also contributes to maintaining an ethical and safe health research environment through its various committees that provide advice on gene technology, approve health and disability ethics committees and institutional ethics committees, monitor the data and safety of large clinical trials and review applications to use new medicines in clinical trials.[84]

## The United States of America

Two key workshop documents were identified in the grey literature regarding clinical trial operation and governance in the USA:

- Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary [85]
- 2. Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary.[93]

Both workshops were conducted by the Institute of Medicine of the National Academies.

The USA had historically been regarded as a good location to conduct clinical trials because of its clinical and scientific expertise and understanding of the research process. However, the USA was losing competitive advantage due to the protracted time from protocol approval to trial activation, and cost burdens. There were also concerns regarding the potential decline in the nation's capacity to conduct clinical trials at a time when demand for them was increasing.

The impetus for convening a public workshop was the need to evaluate the state of clinical research in the USA and identify strategies for enhancing the effectiveness and efficiency of clinical trials. The Institute of Medicine's Forum on Drug Discovery, Development and Translation convened the public workshop on 7-8 October 2009. Through the workshop, clinical trial experts from public, private, academic and industry organisations, patient advocacy groups and pharmaceutical companies came together to discuss current challenges and strategies to improve the efficiency of the clinical trial operating environment. The focus was on randomised controlled trials as they are regarded as the gold standard and foundation of what is commonly referred to as the 'US clinical trial enterprise' (CTE).<sup>19</sup> Clinical trials in four disease areas (cardiovascular disease, depression, cancer and diabetes) were discussed as case studies.

The workshop had three main objectives:

- To examine the state of clinical research in the USA
- To identify strengths and weaknesses in the current CTE
- To consider transformative strategies for enhancing the way clinical research is organised and conducted.

The objectives of the workshop identified the following themes and issues which clinical trials in the USA were facing:

# Barriers affecting the conduct of clinical trials in the USA

- The length of time and high financial costs associated in conducting clinical trials
- Delays associated with navigating the regulatory and ethical requirements of clinical trials
- Difficulties in recruiting and retaining the appropriate patient population
- Fragmentation in the prioritisation of clinical trial operations.

#### Systemic barriers in clinical research

- Discordance between societal priorities and clinical research questions of companies seeking regulatory approval
- The divide between clinical research and clinical practice, including poor translation and the uptake of evidence-based practices by health professionals
- The globalisation of clinical trials, including the trend towards conducting clinical trials outside the USA and the decreasing number of USA patients enrolled in clinical trials
- The costs of conducting clinical trials were reported as higher in the USA than other countries, particularly in Asia, South America and some European countries
- Few incentives for clinicians to participate in clinical research, particularly in private practice
- The high turnover of clinical trial staff as a result of the ad hoc nature of clinical trial work and lack of tenure for research staff was leading to a diminishing clinical research workforce

- Difficulties associated with navigating administrative and regulatory requirements increased the length of time from protocol approval to trial activation. Four key barriers to clinical research were identified as:
  - ethical board approval
  - scientific review/protocol approval
  - interaction with industry and issues with technology transfer
  - adequacy of resources
- Recruitment and retention of patients was affected by the time and effort required to obtain informed consent and satisfy informed consent requirements (including administrative paperwork).

Contributors to the workshop noted undertaking large-scale improvements in the clinical trials enterprise would require leadership and coordination from the highest levels of government. Further, strategic change would need to be informed by an examination of the smaller-scale efforts already under way across the USA. To that end, activities of organisations including the National Center for Research Resources, Clinical Trials Transformation Initiative and the National Institutes of Health (NIH) Roadmap for Medical Research needed to synergise with the CTE. Government leadership of the CTE considered the following as drivers of success:

- Bridge the gap between clinical research and clinical practice through the development of a new framework to better align research and healthcare delivery as well as culture change at all levels of the healthcare system
- Build a strong and stable clinical trial workforce and make clinical trial investigation an attractive career option for academics and health professionals
- Include courses on how to conduct clinical research in the core medical curriculum
- Improve the recruitment and retention of patients through strategies such as providing public education to correct misconceptions about clinical trials and improve the overall perceived value of clinical trials.
A vision for the transformed CTE was proposed by Janet Woodcock (then Deputy Commissioner and Chief Medical Officer of the Food and Drug Administration) based on structural and systemic changes to the way clinical research was to be conducted. The vision was analogous to a national energy grid designed to ensure patients, clinicians and academic researchers all had access to a clinical research system that links research and community practice, facilitates access to a permanent and continuously funded network of resources (e.g. research sites, investigators and support staff) and enables universal participation in the generation of new clinical evidence and its subsequent adoption by physicians.

Investigators participating in the network were organised regionally or nationally around disease or practice areas or 'nodes'. Supporting and uniting the investigators would be core research personnel (biostatisticians, data managers and administrative personnel) and regulatory experts to guide a study through the IRB process. The clinical research infrastructure would be supported through continuous federal funding and the basic funding mechanism would be contracts not grants, thereby overcoming the episodic nature of grants.

Woodcock argued this structure was necessary as the United States Congress and federal agencies administering health programs throughout the country constantly ask which healthcare products and procedures to pay for and the USA Government lacked the capacity to conduct the clinical trials to provide answers to these and other research questions. However, it was unclear who was paying for permanently funded clinical research infrastructure and it was felt that adding a layer of clinical research infrastructure over a fragmented healthcare system would be difficult and potentially ineffective and, as a consequence, was never implemented.

#### Envisioning a transformed clinical trials enterprise in the United States: Establishing an agenda for 2020

The purpose of this subsequent workshop was to determine how to transform the CTE to make it 'efficient, effective, and fully integrated into the overall health system of 2020'. The challenges associated with conducting clinical trials in the USA and jeopardising the viability and strength of the CTE in the USA were reiterated. The core themes in framing an agenda to effect transformation in the USA clinical trials enterprise were identified as:

- Providing a vision for a clinical trials enterprise in the healthcare system of 2020
- Developing a robust clinical trials workforce
- Aligning cultural and financial incentives
- Building an infrastructure to support a transformed clinical trials enterprise.

The overarching or guiding principle was that efforts to transform the CTE were linked to the broader goal of developing a healthcare system for greater adherence to medical evidence for improved quality of care. It was noted that there had been a widening separation in the relationship between the CTE and the healthcare system. The key themes or components of a transformed CTE identified by workshop participants included:

### Convergence of clinical research and clinical practice

- Incorporate clinical research and clinical trials into continuous quality improvement activities of the healthcare system
- Expand research networks and collaborate with professional societies in order to centralise processes and induce more physicians to participate in research
- Reduce the large footprint on clinical practice that research imposes so that it is not overly cumbersome and becomes part of routine practice
- Make research 'business-critical' or 'missioncritical' and an essential component of health services.

## Clinical trial workforce and career development

- Develop research curriculum in medical schools to attract more clinicians to research careers
- Place higher value on clinical trials research in tenure decisions.

#### Public engagement and partnership

- Recognise patients as partners in transforming clinical trials. Consider virtual clinical trial models that use mobile and webbased technologies to conduct clinical trials so that participation in a clinical trial is not dictated by geographical area
- Consider the implementation of a default consent or 'opt-out' process for participation in some types of clinical research
- Recruit participants through online networks
- Provide patients with standardised information on clinical trials and develop a participation card similar to organ donation cards
- Alert clinicians when a patient meets criteria for participation in a trial, using EHRs and clinical trial identifiers; and increase encouragement and advocacy of participation in research by professional medical societies.

#### **Regulatory environment**

- Improve understanding and communication between government regulators and research organisations
- Ease the regulatory environment to reduce the duration and cost of trials to make them more feasible
- Develop greater regulatory harmonisation and simplification. Centralise review boards and update the Common Rule. Ensure patient-friendly repositories of patient data and randomised research projects, especially involving biomarkers and the development of personalised medicine
- Build the USA regulatory framework for codevelopment of new drugs and the devices to administer them
- Provide more flexible FDA and NIH processes for determining type of trial appropriate for a drug investigation phase or research question
- Exempt low-risk research from the IRB process.

#### Cultural and financial incentives

- Create new clinical trial business models that complement advances in technology
- Create template contracts to streamline collaborations and subcontracts
- Correct disincentives for research by providing more coverage for research evidence development (e.g. private payers and Medicare) and reimbursing the routine healthcare costs of research participants
- Develop locally adjusted fee schedules for clinical research tasks, to compensate practitioners
- Fund support for clinical trials.

## Design and develop infrastructure to support clinical trials

- Clinical trials infrastructure currently developed on a trial-by-trial basis
- Online trial infrastructure created through public-private partnerships
- Greater use of research coordinators
- Implement national research labs (similar to those supported by the Department of Energy) with core budgeting and a more engineered system of health learning
- Standardise online training programs and credentialing of investigators
- Provide access to investigator track records (such as, success in recruiting patients to participate in clinical trials and their ability to submit timely clinical trial data to coordinating centres) by research centres conducting clinical trials.

Additional strategies to progress and implement the clinical trials transformation included:

- Incorporate clinical research within the framework of quality improvement programs and striving for cultural change as a business opportunity
- Enlist and engage CEOs of health systems to promote clinical research. CEOs play a crucial role in transforming the CTE by acting assertively to embed research in the mission and culture of the health system, promote clinician training in research and facilitate research projects
- Use electronic health records for research
- Develop research business plans

 Create and maintain research networks organised around specific diseases or discrete health issues or alliances of health services. Networks could provide ongoing credentialing or engagement of researchers.

In 2015, the NIH released its strategic plan for the fiscal years 2016–2020.[94] The strategic plan was designed to harmonise decisionmaking across the agency and situate the NIH's mission and goals in the context of 'tomorrow's challenges and opportunities'. The strategic plan focused on four interrelated objectives: advance opportunities in biomedical research; foster innovation by setting NIH priorities; excel as a federal science agency; and enhance scientific stewardship. The objective of enhancing scientific stewardship comprised seven elements:

- Recruit and retain outstanding research workforce
- Enhance workforce diversity
- Encourage innovation
- Optimise approaches to inform funding decisions
- Enhance impact through partnerships
- Ensure rigour and reproducibility
- Reduce administrative burden.

In 2016, and following on from this report, the NIH launched a multifaceted effort to improve the quality and efficiency of NIH-funded clinical trials referred to as the NIH's stewardship approach to clinical trials. The multifaceted plan aimed to address many of the concerns raised by researchers about the design, efficiency and reporting of clinical trial outcomes.[6] Several initiatives have subsequently been implemented including:

### Revision to the definition of a clinical trial

The rationale for changing the definition was to differentiate between clinical trials and clinical research studies to enhance the precision of the information that the NIH collects, tracks and reports on clinical trials.[95]

#### Good clinical practice training

The NIH holds the expectation that all NIHfunded investigators and staff responsible for conducting clinical trials are trained in GCP to equip them with appropriate knowledge about the design, conduct, recording, analysis and reporting of clinical trials, thereby ensuring the safety, integrity and quality of clinical trials.[96]

## Registering and reporting of clinical trials

This initiative establishes the expectation that all investigators conducting clinical trials (funded in whole or part by the NIH) will ensure that their trials are registered on a publicly available platform (such as <u>www.clinicaltrials.gov</u>) within 21 days of enrolment of the first participant. Further, that results of the trial are also submitted to a publicly available platform.[97]

# Accelerating clinical research by streamlining multi-site review of human subjects research

This approach established the expectation that all sites participating in multi-site studies involving clinical trials (non-exempt) funded by the NIH use a single institutional review board to conduct the ethical review required by the Department of Health and Human Services regulations. The purpose was to enhance and streamline the process of IRB review and reduce inefficiencies so that 'research can proceed as expeditiously as possible without compromising ethical principles and protections for human research participants'.[98]

To facilitate the adoption of this new approach, the NIH National Center for Advancing Translational Science (NCATS) developed a platform – NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform – and standardised resources and agreements to enable institutions to rely on a single IRB record of review for multi-site studies.<sup>20</sup>

### Europe

A report on the ethical review process for clinical trials in the Nordic countries entitled: *The challenges and opportunities of the New Clinical Trials Regulation – A report prepared by the Nordic Trial Alliance Working Group on Ethics* was conducted as a Nordic Trial Alliance's initiative to increase Nordic collaboration and competitiveness in clinical trials.[99] The report presents the review findings on the current ethical review process for clinical trials in each of the Nordic countries and the requirements set out in the new EU legislation on clinical trials. Proposals for achieving harmonisation in Nordic countries are then provided.

The EU Regulation No 536/2014 on Clinical Trials on Medicinal Products for Human Use was the impetus for the reform of current Nordic legislation and practice to support legislative changes and practices of Nordic countries in their assessment of clinical trials. Harmonisation of the procedures for ethical review was to enable the five Nordic countries (Finland, Sweden, Norway, Denmark and Iceland) to form a unified clinical research region for conducting clinical trials. It was anticipated this strategy would improve the competitiveness of the region and make it more attractive to multinational clinical trials by increasing the population base from which to recruit participants for clinical trials, and realise the positive effects clinical trial activity could have on the economy, employment and patient care.

The Organisation for Economic Co-operation and Development (OECD) Recommendation on the Governance of Clinical Trials (2012) is a policy instrument that defines a new framework for improved oversight of clinical trials.[100]

The rationale for acting on the recommendations was the recognition that clinical trials are increasingly evolving from projects conducted at single sites, sponsored by single institutions, into global multi-site collaborative undertakings. The report notes that in the EU nearly 25% of all applications to carry out clinical trials are for multinational clinical trials that are to be conducted in at least two member states. Mononational clinical trials are mostly limited to small studies with low recruitment targets.

The benefits of international collaboration in the conduct of clinical trials identified in the report included faster participant recruitment and greater generalisability of results from different health settings, geographical locations and ethnic groupings. However, it was also noted that the regulatory complexity, diversity and administrative burdens between countries create obstacles for international cooperation in clinical research. Other challenges identified by the OECD included:

- Concern that existing regulatory complexity and administrative issues may lead to some clinical trials being moved away from countries with complex regulatory environments to countries with less stringent regulatory systems in order to save costs
- Clinical trial investigators have had to respond to administrative requirements that are not always adapted to the nature of their study, that is, regulation is not proportionate to the risk posed by the study under review, for example, post-marketing clinical trials which use already marketed products
- There was the need for better ways to align regulations across countries. The idea of a harmonised regulatory framework has therefore emerged whereby requirements would be based on risk associated with the clinical trial at stake. A risk-based approach would facilitate international clinical trials and help streamline the procedures for low-risk clinical trials.

#### Guiding principles for the EU

The recommendation is for members to adopt a risk-based approach to the management methodology for clinical trials. The principles for risk assessment combine a stratified approach (generally based on the marketing authorisation status of the medical product) that can be commonly applied in legislation or regulation across countries, with a trial-specific approach that considers a large number of other issues such as additional diagnostic procedures, specific populations or informed consent.

The OECD Recommendation on the Governance of Clinical Trials also includes interpretation of the stratified risk-based approach to processes such as ethical review; approval by regulatory bodies; informed consent; safety reporting; indemnification and insurance; management of medicinal products; documentation; quality management and control procedures. It also provides a tool with a set of common principles that describe the risk determinants.

## European Union – EU Regulation No 536/2014

On 16 April 2014, the European Parliament and the Council of the EU approved the new EU Regulation No 536/2014<sup>21</sup> of clinical trials on medicinal products for human use. The timing of the application of the regulation is dependent on confirmation of full functionality of the EU clinical trials portal and database through an independent audit. The regulation becomes applicable six months after the European Commission publishes notice of this confirmation. The current estimate for the regulation's entry into application, according to the European Medicines Agency, is the latter half of 2019.22 When it comes into use, the new regulation will replace the Clinical Trials Directive (Directive 2001/20/EC) which was widely criticised as increasing the regulatory burden and costs of conducting clinical trials in the EU. It is claimed that this over-bureaucratisation contributed to Europe's decline as an attractive clinical trial destination, as reflected in the significant reduction (25%) in the number of trials conducted in Europe between 2007 and 2011.[101] The aims of the new regulation are to ensure patient safety, improve clinical trial transparency, simplify the application process for clinical trials across EU member states and re-establish the EU's competitiveness in clinical trials and pharmaceutical development.[102]

There are several key differences between Directive 2001/20/EC and Regulation 536/2014. The new regulation will have binding legal force in all EU member states whereas under the directive, it was each member state's responsibility to implement the contents of the directive in their own national laws. Thus, different interpretations of the document resulted in slight discrepancies between the laws of each member state. Also, the authorisation of a clinical trial was specific for each member state.[103]

While a directive is a legislative act that sets out a number of goals that all EU member states must achieve individually through changes in their own national legislation, a regulation is a binding legislative act, immediately applicable and enforceable in the whole EU, and thus has a legislative power comparable to a law. Sponsors and investigators for clinical trials taking place in multiple member states can rely directly on the new regulation, as opposed to dealing with each member state's individual approach to an EU directive.[103] A major criticism of Directive 2001/20/EC was that it only partially achieved the goal of simplifying and harmonising the scientific and ethical review of clinical trials in the EU.[103] Under the directive all member states assessed the request for authorisation of a multinational clinical trial independently of one another. This was particularly problematic when conducting clinical trials across several member states as multiple submissions of largely identical information were required. The regulation aims to overcome this barrier by introducing a system whereby only one application dossier will be submitted to an individual member or multiple member states where applicable, via a single EU submission portal and database.

A key part of the new regulation is the EU-wide portal and database which will provide a single point of entry for all clinical trial applications across the EU. All information in the EU database will be publicly accessible unless its confidentiality can be justified, for example, the protection of commercially confidential information or protection of personal data. The portal will be the single-entry point for submitting clinical trial information in the EU, which will be stored in the database.

The regulation also introduces the concept of a low interventional trial which is defined as a clinical trial that fulfils all of the following criteria: the medicinal product has market authorisation; poses no more than a minimal additional risk compared with normal clinical practice; and the medicinal product is being used within the market authorisation (or the use is based on published scientific evidence). An example would be testing a medication that has market authorisation for a new indication. This allows for a more risk-based approach to the approval of clinical trials to be taken.

To simplify and speed up authorisation of clinical trials, the European Commission has decided that the risk-benefit assessment (and the preceding scientific assessment) should be performed in a coordinated manner. With this in mind, sponsors propose one member state to have the role of reporting and making the final decision on the risk-benefit assessment. The other member states are asked for their input but within a very tight timeframe. The main task of the reporting member state is to assess the ethical and local aspects such as the informed consent material, the investigators' qualifications and the suitability of the trial site for their own territory. Thus, two types of assessment run in parallel: the coordinated risk-benefit assessment (by the reporting member state, binding on all member states) and the assessment of the ethical and local aspects (by all member states acting individually).[104] Several criticisms have been levelled at this process:

- As argued by several authors, the risk-benefit assessment is taken out of the ethical domain. As a result, the regulation does not require input from an ethics committee. This is of concern because the purpose of ethics committees is to protect participants from potential harm [103,105,106]
- Assessing risk in comparison with the standard treatment of the subjects' condition raises the possibility of exploiting vulnerable research participants.[107] Where the standard treatment poses substantial risk there is the potential to exceed the levels set out in international guidance such as the Declaration of Helsinki
- Sponsors are free to choose the reporting member state. This might tempt sponsors to choose member states that are known for their less onerous assessments
- There is also debate between critics of the regulation. While some believe that the regulation is still overly bureaucratic and impedes research, others argue that the clinical trials regulation swings too far in the favour of facilitating research thereby exposing trial participants to unacceptable levels of risk.[101]

#### **Clinical trial governance**

Under the new regulation the responsibilities of member states include:

- Authorisation and oversight of clinical trials
- Determination of the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial
- Organising the review of a clinical trial by an ethics committees within the timelines for the authorisation as set out in this regulation
- With regard to civil and criminal liability, each member state has the choice as to whether a sponsor that is not established in the EU requires legal representation should enforcement action be taken
- Member states should ensure that systems for compensation for damages suffered by a subject are in place, which are appropriate to the nature and extent of the risk

- If, during a clinical trial, damage is caused to a subject and this leads to civil and criminal liability of the investigator or sponsor, the conditions for liability (including issues of causality and the level of damages and sanctions) should remain governed by national law
- The member state concerned should be given the power to revoke the authorisation of a clinical trial, suspend a clinical trial or require a sponsor to modify a clinical trial
- In order to ensure compliance with this regulation, member states should be able to conduct inspections and should have adequate inspection capacities.

## Responsibilities of the European Commission

The European Commission should be able to control whether member states correctly supervise compliance with the regulation. Moreover, the European Commission should be able to control whether regulatory systems of third countries ensure compliance with the specific provisions of this regulation and Directive 2001/83/EC concerning clinical trials conducted in third countries.

#### Responsibilities of the European Medicines Authority

The European Medicines Authority has the responsibility of creating and managing the EU portal and database and supervising content publication on the public website.

#### **Responsibilities of sponsors**

The regulation requires sponsors to:

- Adequately monitor the conduct of a clinical trial
- Give notifications when:
  - ► a trial begins
  - a subject first visits the trial
  - a trial is temporarily halted
  - a trial is terminated early
  - a trial ends.

**Figure 3**: Overview of the European approach to clinical research governance





#### Legislative basis

The regulation is in line with the major international guidance documents on clinical trials such as the 2008 version of the World Medical Association's Declaration of Helsinki and Good Clinical Practice, which has its origins in the Declaration of Helsinki. This regulation is based on the double legal basis of Articles 114 and 168(4)(c) of the Treaties of the European Union. The regulation aims to achieve an internal market for clinical trials and medicinal products for human use, taking as a base a high level of protection of health. At the same time, the regulation sets high standards of quality and safety for medicinal products to meet common safety concerns regarding these products. Both objectives are being pursued simultaneously. These two objectives are inseparably linked, and one is not secondary to another.

#### The Nordic Alliance

In all five Nordic countries, the legal framework for ethics committees includes both legislation and statutes/regulations. The basic operating principles and functions of ethics committees in each Nordic country are similar and conform to the definition in the EU Regulation. The ethics committees are mandated by law; they must be independent; and their main task is to review the ethical aspects of different kinds of medical research involving human subjects. The countries vary as to whether these tasks are assigned to regional ethics committees alone or divided among regional and national committees.

The EU Regulation No 536/2014 is legally binding in all Nordic countries due to the European Economic Area relevance of the regulation. However, the regulation only establishes certain common general requirements for legislation and practices regarding ethical evaluation of clinical trials on medicinal products, thereby leaving the question of how to implement these requirements largely up to the member (and associated) states. Therefore, the regulation does not necessarily prevent differences in national practices. The models proposed for ethical review were:

- A joint, centralised supranational ethics committee for all five Nordic countries. All multinational clinical trials on medicinal products planned in the Nordic countries would be delegated to the joint Nordic committee for ethical review. National committees would still need to be maintained to review clinical trial authorisations submitted from individual countries
- Mutual recognition procedure. One country would perform a thorough ethical review of the clinical trial authorisations and other Nordic countries would automatically accept and recognise the conclusions or results of the review. It was noted that this would require trust in each other's committees and systems
- Maintain the evaluation at the national level. Reform the legislation and procedures in each country in a coordinated manner in order to harmonise the procedures. A supranational Nordic body would provide coordination, document templates, education and guidance. The requirements and standards of the ethical review would have to be agreed upon between countries.

It was noted that regardless of the option chosen, the basis of the harmonisation would be the documentation required for the assessment process. The documentation would be standardised and agreed in advance, thereby preventing any country from requiring additional documents to clarify aspects of the research protocol, unless agreed between the countries. Similarly, the assessment procedures would also need to be harmonised to ensure that applications are processed in the same way across all Nordic countries.

In relation to the appeal process, the bodies of appeal would be maintained at the national level. In terms of implementation, systemic changes should be governed by duly appointed and mandated officials so that the legal validity and practical implementation of the changes can be guaranteed – voluntary harmonisation by independent ethics committees being considered unlikely to be successful.

The report concluded that if harmonisation is achieved and proves to be functional, it could serve as a model for harmonising the procedures in other areas of medical research as well, paving the way towards a common Nordic research area in clinical research.

### **Section summary**

In this section, the peer-reviewed and grey literature highlighted factors identified as barriers to the efficient and effective operations of clinical trials in Australia and internationally, and the processes undertaken by several countries to improve their local clinical trial environments.

New Zealand has implemented a national approach to clinical trials governance, with responsibility for the implementation resting with the Minister of Health and the Minister of Science and Innovation through the Health Research Council (HRC). The national implementation strategy embeds clinical trials into the health service delivery functions of the DHBs. While initiatives are under way to streamline clinical trial approval processes in the Nordic region, in Europe the disparate application of legislation relating to the conduct of clinical trials has led to a lack of cohesion in ethical approval and regulatory processes between member nations. In the USA, central coordination of a national strategic approach to clinical trials governance is recognised as being necessary to implement large-scale improvement. This approach is problematic due to fragmentation and the nature of the health system (user-pays). Smaller-scale initiatives are under way, driven by organisations such as the National Institutes of Health Center for Advancing Translational Sciences in collaboration with the Clinical Trial Enterprise, to drive change through their funded members for streamlined processes, standard agreements and resources platforms.

Further to these insights, Section 4 presents an overview of the national approaches to improving the governance of clinical trials with focused insights from Canada, the UK and South Korea, followed by an overview of the Australian clinical trial environment and local approaches to improving clinical trial operations.

# **Section 4: Countries in focus**

### Key messages

- The clinical trial governance framework in the United Kingdom is underpinned by legislation (Health and Social Care Act 2012) and supported by the United Kingdom Policy Framework for Health and Social Care Research and an operational framework, the Research Support Services Framework. The Health Research Authority provides regulatory oversight and the national approach is implemented through the National Institutes of Health Research (NIHR). The NIHR is responsible for funding, infrastructure and the national coordination of the clinical research networks located in 15 geographic locations through which clinical trials are managed and conducted
- South Korea has a highly centralised approach to clinical trial governance with oversight by the South Korea Department of Health and the Ministry of Food and Drug Safety, and underpinned by the South Korea Health Industry Development Institution Act 1999. The Korea National Enterprise for Clinical Trials (KoNECT) was established in 2007, to streamline the regulatory approval process, establish a network of excellence in clinical trial sites and to facilitate engagement with national and international partners through the KoNECT Collaboration Centre.

This is a one-stop shop for the efficient conduct of clinical trials, providing global networking, local-site accreditation, trialsite staff training and resources, patient and consumer information, measures of operational performance and access to patient-level data to facilitate participant screening and recruitment to clinical trials

- Canada established the Canadian Clinical Trials Coordinating Centre in 2012 to coordinate improvements across the clinical trials sector through the provincial national disease and treatment networks. Canada's public health system comprises 10 interlocking provincial and three territorial health systems. Health Canada is the authority responsible for clinical trial approvals, oversight and inspections and operates under the Canadian Food and Drugs Act. The CCTCC failed to align local clinical trial operational improvement initiatives under way in the provinces to establish a national approach to clinical trials governance
- Australia, the UK, South Korea and Canada have universal healthcare systems and the capacity to implement a national clinical trials governance framework. The Canadian experience has resonance for Australia. In the first instance, engaging the jurisdictions to implement clinical trial reform will be achieved through a national accreditation scheme for clinical trials.

### Canada

Canada's public health system comprises 10 interlocking provincial and three territorial health systems. Canada has a universal health system (Medicare). Canada's hospitals are linked via provincial or national disease-treatment networks that help to coordinate research across specific centres of expertise.<sup>23</sup> Under Canadian legislation (Canadian Food and Drugs Act; Food and Drugs Regulation; and the *Guidance*  *Document for Clinical Trial Sponsors: Clinical Trial Applications*) Health Canada is the authority responsible for clinical trial approvals, oversight and inspections.<sup>24</sup>

There are five geographic clusters of clinical trial sites: Atlantic Canada, Ontario, Central Canada, Quebec and British Columbia. Approximately 5,000 clinical trials were conducted in 2016 and Canada has the second lowest cost among Group of Seven (G7) nations in the management, design and coordination of global clinical trials.[108]

### Clinical trial initiatives to incentivise the environment

The Canadian Clinical Trials Summit of 2011 was convened following a decline in clinical trial activity in Canada to find ways to improve Canada's competitiveness in attracting clinical trials in the face of emerging global challenges. [109] Canada had experienced a decline in clinical trial applications for non-generic drugs from 777 applications in 2006 to 596 applications in 2010. Although there was a decline in Phase I and Phase II clinical trials, the decline was most notable in Phase III trials.

A multi-sector steering committee (comprising academia, health care, industry and government) was engaged to lead the summit in developing a national strategic action plan. The summit considered Canada's track record of world-first medical discoveries; public interest in clinical trials; the reputation of researchers, research organisations and research outcomes; the quality of clinicians and clinical practice; the publicly funded healthcare system; and national and provincial healthcare leadership. It identified operational barriers (such as administrative issues, cost structures, non-standard contracts and diverse ethics committee standards) that could compromise the proposed action plan. Other issues such as population size, difficulties in patient recruitment and retention, trial costs, data quality, staff training and capacity issues were also cited as challenges to Canada's strategic planning for change. The summit released a series of 28 action items across the following areas of clinical trials [110]:

- Ethics reviews
- Patient recruitment
- Administrative structures
- Cost issues
- Strategic infrastructure.

In 2014, the Canadian Clinical Trials Coordinating Centre (CCTCC) was established and the national action plan *To Your Health and Prosperity... An Action Plan to Help Attract More Clinical Trials to Canada* was issued. The CCTCC held a 3-year mandate to progress the implementation of initiatives arising from the action plan.[111,112]

The action plan was developed with the assistance of the major stakeholder groups (Canadian Institutes of Health Research, Canada's research-based pharmaceutical companies, Association of Canadian Academic Healthcare Organisations). The aim of the action plan was to 'collectively assist clinical trial companies to succeed, and in so doing, generate the human, social and economic benefits of clinical trials'. The primary focus for implementation of the action plan was publicly funded clinical trial sites and commercial pharmaceutical, vaccine and device companies. The intention of the CCTCC was to coordinate and leverage common solutions wherever possible and to benefit all clinical trial stakeholders, by expanding this focus to clinical trial improvement activities. Several risks to implementing the action plan were identified, namely inaction and stakeholder uncertainty as to whether they could 'mobilise, organise and accomplish what they had set out to achieve'. The costs associated with staffing and coordinating the implementation of the plan were also considered.

The action plan contained three goals and nine recommendations expressed through an underlying logic model (Figure 4). The recommendations are provided at Appendix 1, Table 7.

The goals were to:

- Halt and reverse the downward trend in clinical trial investment
- Improve business practices as they pertain to clinical trial operations
- Create a stable, forward-looking opportunity for clinical trials into the future.

#### Figure 4: Logic model

#### If we address...

- Ethics
- Recruitment
- Cost structure
- Admin issues
- Infrastructure
  - Innovation

#### We improve...

- Cost
- Quality
- Speed
- Relationships

#### Which attracts...

Clinical trials

#### Resulting in...

 Human (health), social and economic benefits

#### Implementation strategies

Three implementation strategies were outlined within the CCTCC's action plan. These included:

- Establish a national presence for implementing and coordinating clinical trial improvements that would coordinate provincial activities, implement performance measurement and management, provide support and direction for the clinical trial initiatives and clearly articulate the roles and responsibilities of all stakeholders
- Improve business operations with better cost, quality and speed of clinical trial start-up times. This would require streamlining ethical review of clinical trials, strategies to improve patient recruitment such as registries, the development and implementation of standard operating procedures, staff training and certification, and a standard clinical trial agreement
- Signal (globally) Canada's interest in clinical trials through opening a national concierge service for clinical trials, and implementing changes in intellectual property protection and scientific research and experimental development tax credits.

#### Canadian clinical trial agencies

Several national agencies have been involved in developing initiatives and implementing strategies designed to improve and strengthen the Canadian clinical trials sector.

#### The Canadian Institutes of Health Research (CIHR)

The CIHR is the Canadian Government's health research investment agency responsible for funding health research in Canada. It invests approximately \$1 billion each year to support two types of research: investigator-driven and priority-driven. The CIHR is an independent agency created in 2000 under the authority of the Canadian Institute Health Research Act and is accountable to parliament through the Minister of Health. The mandate of the CIHR is to 'excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system'.

The CIHR supports four pillars of health research: biomedical, clinical, health system services and population health. The CIHR integrates research into the health system through an interdisciplinary structure comprised of 13 virtual institutes or networks of researchers, with each institute focusing on a specific health research area (e.g. infection and immunity, cancer research), systems services and population health.[113]

#### Canadian Clinical Trials Coordinating Centre

The CTCC is a pan-Canadian clinical trials organisation established in 2014 in response to emerging global challenges to Canada's clinical trial competitiveness. It is a collaboration between the CIHR, Innovative Medicines Canada and HealthCareCan. The CTCC's overarching aim is to facilitate pan-Canadian collaborations. Its mission is to improve the clinical trial landscape and Canada's global competitiveness by promoting operational efficiencies and advocating streamlining of clinical processes for both industry and clinical researchers. An advisory group comprising experts in the clinical trial field provides direction and input on projects and initiatives. Since its inception, the CTCC has been involved in developing several initiatives as a result of the recommendations contained in the 2014 Clinical Trials Action Plan. Some of these projects have been finalised and implemented, while others remain in the development phase including:

- The Canadian Clinical Trials Asset Map a searchable, web-based database designed to showcase and communicate Canada's clinical trial assets to potential sponsors and facilitate easy identification of clinical research sites and investigators
- The Patient Registries Listing Project designed to facilitate and improve patient recruitment to clinical trials and complement the Canadian Clinical Trials Asset Map
- The Fair Market Value Project aimed at providing tools and resources for a more streamlined and efficient process for negotiating and funding budgets for clinical trials
- The Model Clinical Trials Agreement a standard model contract for use by clinical trial sites and sponsors in negotiating clinical trial agreements
- An investment case entitled Clinical Trials: The Canadian Advantage to showcase Canada as an attractive clinical trials destination

- The Clinical Trials Metrics Platform a suite of operational metrics to monitor organisational efficiencies (e.g. timeliness of contract and budget negotiations, research ethics boards' approval processes)
- The Research Ethics Boards (REB) Accreditation Project – a CTCC Research Ethics Board Accreditation Working Group was formed in 2015 to review REBs and identify opportunities to improve efficiencies through REB centralisation, harmonisation and accreditation of these boards. A key recommendation proposed by the working group was to establish a national strategic leadership forum to champion, shape and direct the development of research ethics on a pan-Canadian level. This issue is discussed further below
- Supporting provincial collaboration in 2015, the CTCC facilitated the first joint meeting of provincial clinical trials organisations to identify emerging issues and challenges in the clinical trials sector, as well as foster collaboration in project engagement, and prevent duplication of effort.[114,115]

Towards the end of the CCTCCs 3-year mandate in 2017, an independent 2-phase strategic consultation was conducted with key stakeholders to review CTCC's performance and to establish the direction for future planning needs. Several deficiencies of the CTCC were noted during the consultation process, including insufficient communication of CTCC's clinical trial initiatives and achievements. A key strategic challenge for the future pan-Canadian clinical trial strategy was also identified as being the broad range of clinical trial initiatives being undertaken at the local, provincial and national level, which was often resulting in duplication of effort. The critical issue identified by the review was the continued need for a pan-Canadian coordinating organisation (either the CCTCC or a new organisation) to address challenges and facilitate efforts to improve the Canadian clinical trials landscape.[116]

#### The Network of Networks

The Network of Networks (N2),<sup>25</sup> established in 2008, is a not-for-profit incorporated organisation, an alliance of Canadian research networks and organisations working to enhance national clinical research capability and capacity. N2's membership comprises approximately 100 organisations representing over 3,000 clinical research professionals, from over 200 sites across numerous therapeutic disciplines. The N2 acts as a national voice on issues affecting or influencing clinical research in Canada and serves as a national alliance to bridge regional and provincial initiatives. The aim of the N2 is to enable and enhance Canadian clinical research capability and capacity, and improve the efficiency and quality of clinical trials conducted in Canada.[26]

The N2 Network of Networks website provides information and a range of resources pertaining to clinical trials including:

- Itstartswithme This is a web-based resource designed to provide potential clinical trial participants, caregivers, family members and the general public with basic information about clinical trials. The website includes videos, postcards to help participants start a conversation with their healthcare providers about research, and a Research Participants' Bill of Rights
- Professional clinical research education and training programs – These include Good Clinical Practice and Responsible Conduct of Research
- Standard operating procedures Standard operating procedures for research ethics boards have been developed in conjunction with the Canadian Association of Research Ethics Boards together with standard operating procedures for biospecimen handling which have also been developed by the N2 organisation.

#### The Canadian Association of Research Ethics Boards

The Canadian Association of Research Ethics Boards<sup>26</sup> was established in 2010 as a grassroots Canadian membership organisation intended to represent the interests of all Canadian research ethics boards. The membership comprises research ethics board professionals; namely chairpersons, members and administrators of research ethics boards.

## Canadian research ethics policies and processes

The national framework for conducting research involving humans is Tri-Council Policy Statement for Research Involving Humans developed by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada. This policy provides guidance on the interpretation of the principles of research ethics and serves as a benchmark for the ethical conduct of research involving humans across Canada. There are several mandatory requirements for researchers, institutions and members of research ethics boards, and adherence to the policy is a condition of funding for those researchers and organisations that receive funding.[21]

**Health Canada** 

responsible for clinical trials approvals, oversight and inspections

The authority

A major focus for Canada has been attempting to centralise, harmonise and improve research ethics board efficiencies at the national or pan-Canadian level. Currently, there is no centralised or single-entry point to lodge ethics applications in Canada; however, some initiatives have been undertaken at the provincial level to streamline ethical review processes and strengthen their respective clinical trial sectors (Table 5).[22]



Province	Organisations and initiatives
Alberta <sup>27</sup>	The Health Research Ethics Harmonization Initiative aims to provide a streamlined, effective, collaborative and integrated model for ethics reviews
	Alberta Clinical Research Consortium
	Health Research Ethics Board of Alberta brings together three former research ethics board as a committee operating as one research ethics board
British Columbia <sup>28</sup>	Clinical Trials British Columbia – which is part of the British Columbia Academic Health Science Network (BC AHSN)
	BC Ethics Harmonisation Initiative – collaboration between eight partner organisations. Harmonised ethical review model comprising BC Reciprocity Agreement; Harmonised Minimal and Above Minimal Risk Ethics Review Models
	Canadian Clinical Research Participation Survey
Ontario <sup>29</sup>	Clinical Trials Ontario (CTO)
	Province-wide, <b>streamlined research ethics review system</b> that supports a single ethical review for multi-centre clinical trials
	The single review can be undertaken by any qualified research ethics board in Ontario, on behalf of multiple institutions
	16 qualified research ethics boards
	~80 participating sites
	Electronic, online submission process
Quebec <sup>30</sup>	Quebec Ministry of Health and Social Services, Multi-Centre Research Ethics Review Mechanism. Single research ethics board review for multi-centre research studies
	CATALIS Quebec Clinical Trials, formerly known as the Early Stage Clinical Trials (ESCT) initiative. This organisation is financed by the Quebec Government and industry members and was established with the aim of making Quebec a globally recognised hub for early-stage clinical research
New Brunswick <sup>31</sup>	New Brunswick Health Council Research Ethics Board Horizon Health Network and Research Ethics Board Vitalite – provides research ethics board reviews for all hospitals in the region by both paper and electronic means
Nova Scotia <sup>32</sup>	Nova Scotia Health Authority: Nova Scotia Health Authority research ethics board
Newfoundland and Labrador <sup>33</sup>	Health Research Ethics Board of New Foundland and Labrador
Saskatchewan <sup>34</sup>	Saskatchewan Academic Health Sciences Network

Table 5: Clinical trials initiatives introduced by Canadian provinces

#### **Successes and failures**

Several reviews and reports, such as the Strategy on Patient-Oriented Research, the External Advisory Committee on Streamlining of Health Research Ethics Review 2013 (SHRER) [23] and the 2012 Action Plan [24] put forward recommendations to improve multi-site ethics review, with little effect. Similarly, efforts to establish a national program for the assessment of human research have stalled. The Canadian Clinical Trials Coordinating Centre Research Ethics Board Accreditation Working Group was formed in 2015 to review and assess the current situation regarding research ethics boards and to identify strategies to improve efficiencies of ethics reviews, such as a system of research ethics board accreditation.[25] The major findings have been included in this literature review because they could apply to Australia given the federal structures of both countries. The two factors identified by the working group to explain the failure of previous efforts were, firstly, the lack of leadership and clear authority to undertake the required consultative work and to provide the practical support necessary to implement any proposed assessment and governance model. The working group cited the example of the United Kingdom (UK) as a potential model noting that the UK has had the support and endorsement of a combined group of stakeholders in the Health Research Authority. The working group noted that, in the absence of national leadership in Canada, many provinces have implemented their own strategies to streamline ethics review, resulting in a diversity of harmonisation and streamlining processes. The working group argued that a coordinated national approach was needed to align initiatives and facilitate pan-Canadian communication and collaboration. A strategy echoed by the N2 similarly noted that the challenge for Canada now is to leverage the provincial initiatives at the national level to create synergies and avoid duplication of effort by other provinces.[26]

Secondly, the working group cited a persistent lack of funding and leadership for the development of a system for assessment and enhancement of research ethics board functions. Several real or perceived barriers to extending research ethics board jurisdiction beyond provincial borders and implementing single and/ or central research ethics board review of multijurisdictional studies across Canada were also cited. These included legislative variations across provinces particularly relating to provincial privacy legislation; concerns over institutional liability issues; and other administrative and riskmanagement issues.

The primary recommendation of the working group was for a national strategic leadership forum to be established to champion, shape and direct the development of research ethics at a pan-Canadian level. Further, a research ethics governance model and authoritative leadership group is necessary if efficiencies in ethics reviews are to be implemented on a national basis. The working group concluded that a national strategic leadership forum would be the most appropriate in the Canadian context given its federal nature and the fundamental constitutional divisions that exist leading to a collaborative and federal model for ethics leadership in Canada. The working group also noted the lack of evidence on the effect of accreditation in improving research ethics boards and therefore advised the accreditation

solution required further consideration.[25]

In summary, a central feature of Canada's governance framework has been the establishment of a government-funded central coordinating agency charged with the remit of actioning the recommendations arising from high-level reviews into the national clinical trials sector. While the CCTCC successfully implemented several programs to improve and strengthen clinical trials and promote Canada as an attractive clinical trials destination, it was unsuccessful in facilitating a pan-Canadian approach to harmonising, streamlining and centralising the clinical trial ethical review process. In the absence of strong national leadership, jurisdictions have independently made significant progress to improve the efficiency of ethical review at the local level. The need to leverage jurisdictional initiatives and create synergies at the national level to avoid wastage of resources and duplication of efforts could be relevant to Australia.

### **United Kingdom**

#### A governance framework for clinical trials in the United Kingdom

'It is critical that research is seen as core business in the National Health Service (NHS).' — Professor Steve Robson, Newcastle Upon Tyne Foundation Trust<sup>35</sup>

Over the past 10 years significant improvements have been made to clinical trials and health research in the United Kingdom (UK).<sup>36</sup> KPMG estimated that in the period April 2014 to March 2015 clinical research activity supported by the National Institute Health Research (NIHR) Clinical Research Network (CRN) generated a total of £2.4 billion (A\$4.4 billion) and supported almost 39,500 jobs. The amount of £1.6 billion was for commercial activity and £21 million as a result of the CRN Coordinating Centre's activities.[117] This equated to NHS trusts receiving an average of £6,658 (A\$12,200) in revenue per patient from commercial sponsor companies.[117] Industry invests over £5 billion (A\$9.2 billion) annually in healthcare research.

In the 2016–17 financial year, 65% of NHS trusts increased their research activity,enabling more than 665,000 individuals to participate in clinical research through the NIHR clinical research network, an increase of 10% on 2015–16.[118] Approximately 35,000 participants were recruited to studies sponsored by the life sciences industry (clinical trials and clinical research projects). More than 11,000 research staff are funded by the NIHR, including more than 5,000 nurses.<sup>37</sup>

There are a number of key organisations that support research in the UK (Figure 6). Several of these are government organisations under the umbrella of the National Health Service (NHS) including: the NIHR; the NIHR Office for Clinical Research Infrastructure (NOCRI); and the NIHR Clinical Research Network Coordinating Centre and Clinical Research Network (CRN).

Other government organisations include the Medical Research Council (MRC) and Research Councils UK. A newly emerging entity is UK Research and Innovation. When it comes into effect in April 2018, UK Research and Innovation will bring together seven research councils, Innovate UK and a new organisation, Research England. It will operate across the whole of the UK with a combined budget of more than £6 billion (A\$12 billion).<sup>38</sup>

There are also non-departmental and independent organisations – the Health Research Authority; the UK Clinical Research Collaboration (UKCRC); The National Institute for Health and Care Excellence (NICE) and the Office for Strategic Coordination of Health Research. In addition, there are several major research charities including the Wellcome Trust and Cancer Research UK; six designated academic health sciences centres and a number of university partners.

#### **Historical perspective**

In 2010, in anticipation of the general elections, the Academy of Medical Sciences (the UK's leading medical scientists from hospitals, academia, general practice, industry and public service) published a guiding document outlining its proposal or vision for UK medical science. [119] The central tenet of the academy's position statement was that medical science offered the next UK Government an unprecedented opportunity to reinvigorate the economy and enhance the productivity of the NHS. The strengths of the UK medical science and research sector (including internationally renowned academic medical research centres, skilled researchers, flourishing pharmaceutical and biotechnical companies, and a unified health system) presented a significant advantage for both basic and clinical research. However, a great deal of clinical trial activity had already moved abroad as evidenced in the decline in the UK's share of the world's clinical trial activity which fell from 6% to 2% between 2000 and 2006. The academy proposed that the UK needed to firstly tackle seven important challenges to address this decline, as summarised below.

The research potential of the NHS remains unfulfilled. The NHS needed to become a willing participant in health research in order to benefit patients. It was possible to achieve this by including high-quality research as an integral component of the next NHS Operating Framework including outcomes on which the performance of NHS trusts is measured. Research should be made a central goal of any NHS system for electronic health records. This was to allow researchers access to data to improve the safety of medicines, to better understand the causes of disease, to identify research participants and to locate patients who would benefit most from targeted health interventions.

The regulatory environment is a driver for medical science abroad. Data protection regulations were viewed as a serious impediment to medical research without providing significant benefit to patients. It was recommended that streamlining and improving current regulation represented a cost-effective approach to creating a more fertile and productive research environment. A proportionate, risk-based regulatory framework for medical research involving patients, fit for purpose and informed by an independent review of existing regulations was recommended.

Innovative incentives underpin the medical science industries in the UK. The review proposed consideration of a range of instruments to drive research and development investment including flexible pricing, public procurement strategies, tax incentives, and new pathways to support uptake and access to medicines. Formation of alliances should also be encouraged between the NHS, universities and industry, to share the risk and reward associated with generating more costeffective and novel therapeutics, diagnostics and devices.

Publicly funded health research requires further coordination. Public investment in medical research needs to be sustained and delivered in a coordinated fashion. Strategies recommended included guarantining the budgets held by the Medical MRC and the National Institute for Health Research (NIHR) and protecting and building on the successes of the Office for the Strategic Coordination of Health Research to ensure basic biomedical and translational science is managed in a coordinated fashion. It was recommended that the UK should also strengthen health research by maintaining and enhancing coordination of the MRC and NIHR, in close collaboration with the NHS. The relationships with other scientific disciplines, industry, charities and the devolved administrations are crucial determinants of a successful health research agenda.

Public health challenges must become crossdepartmental priorities. Budgets and strategies needed to be developed for specific public health priorities such as obesity, alcohol, ageing, infectious pandemics and climate change, which were noted to cut across departments.

Health research should be used as a driver of foreign policy and international development. Health research should be central to UK foreign policy and should underpin all efforts to tackle disease in resource-poor countries. Greater efforts are made by the UK Government to support indigenous research capacity in

resource-poor countries.

The UK must grow and sustain its world-class biomedical workforce for the knowledge economy. Recommendations proffered by the academy to achieve this goal included promoting and supporting biomedical research training for doctors and other healthcare professionals in the NHS, and incentivising the mobility of researchers across academic, industry and healthcare sectors.

## Reports of reviews on clinical trial operations in the UK

Following the Academy of Medical Sciences document [119] the Department of Health for England commissioned the academy to conduct an independent review of the regulation and governance of health research in the UK. The results of that review (known as the Rawlins Review) were published in 2011: *A new pathway for the regulation and governance of health research.*[120] The terms of reference for the review were to:

- Conduct a review of the regulatory and governance environment for health research in the UK with a particular focus on clinical trials
- Identify key problems and their causes, including unnecessary process steps, delays, barriers, costs, complexity, reporting requirements and data collection
- Make recommendations with respect to the regulation and governance pathway that will achieve the following: increase the speed of decision-making; reduce complexity and eliminate unnecessary bureaucracy and cost.

In making recommendations for change, the need to ensure the protection of participants, as well as the need for appropriate arrangements for governance and accountability, were considered central.

The focus of the review was the prevailing regulation and governance pathway for health research and clinical trials in the UK. The system was fragmented and complex, with multiple layers of bureaucracy, duplication and overlapping responsibilities. The final report from the review noted that not only was there a lack of trust in the current regulatory and governance system, but there was also no evidence that these measures had enhanced the safety and wellbeing of either patients or the public.

The review confirmed previously identified system-level barriers and highlighted that the governance arrangements within NHS trusts were the single greatest barrier to health research. Other issues pertaining to the regulation of health clinical trials were also identified:

**Delays and duplications** in obtaining research permissions from NHS trusts. The system was thought to be inefficient and inconsistent, characterised by NHS trusts reinterpreting assessments already undertaken by the National Research Ethics Service, and duplicating checks that could be done once across a study. The practices of research and development offices were developed in response to the Research Governance Framework for Health and Social Care. Local negotiation of research contracts and costings, and a lack of agreed timelines for approvals, were cited as a further source of delay. **Complexity and inconsistency** across the regulation pathway has meant researchers needed to navigate numerous approval and permission processes, coordinated by multiple bodies with overlapping responsibilities. Approval processes were often undertaken in series rather than in parallel, and conflicting advice by regulatory bodies led to inconsistency, confusion and variable standards.

Lack of proportionality in the regulation of clinical trials has meant the broad scope and 'one size fits all' approach of the EU clinical trial directive was thought to place an unnecessary burden on clinical trials testing of new products and new therapeutic interventions, and comparative effectiveness clinical trials of registered products and interventions. There were also concerns raised about the interpretation of the EU directive.

Lack of evidence that the regulatory and governance environments have individually or collectively enhanced the safety or wellbeing of either patients or the public.

Other barriers or impediments to health research and clinical trials cited in the review included:

**Constraints on access to patient data** was believed to be impacted by a fragmented legal framework leading to inconsistency in interpretation of the regulations, variable guidance, and a lack of clarity among investigators, regulators, patients and the public.

**Research afforded a low priority by NHS** trusts and a prevailing healthcare culture that failed to fully support the value and benefits of health research. The focus of NHS managers was identified as meeting immediate healthcare targets but there were few equivalent incentives to encourage support from NHS staff for health research. There was also the perception among NHS managers that health research conflicts with managerial goals for service delivery because research requires resources such as staff time and access to facilities and equipment. This problem was compounded by tensions between short-term NHS targets and the longer-term nature of research, and its impact on clinical practice. While acknowledging that clinical services are a priority, the review proposed a need for change in the attitude and behaviour of NHS managers. It was also important that NHS managers recognise that research is an essential component of good evidenced-based clinical service provision.

**Professionals lack time and incentives to become involved in research**. Related to this, was the argument that research needed to be core business.

**Research is not considered a core NHS activity in the UK**. The review contended that research needed to be formally and irreversibly embedded in the NHS leadership and governance processes. However, the review also identified that broadscale cultural change was required before research would be considered or treated as a core NHS activity throughout the UK. The role of health research in the delivery and improvement of NHS care was the responsibility of health service management staff at all levels in the NHS.

#### Risk averse culture towards research

highlighted what it termed the 'prevailing risk averse culture' towards research which led to an over cautious approach to research in many NHS trusts. This was evident in the time taken to approve individual research studies and the duplication of minor checks and administrative processes.

## Recommendations from the Rawlins Review

This report outlined a vision for regulation and governance and identified four principles to assess against the current regulatory framework and to test the proposals for change. The four guiding principles were:

- Safeguard the wellbeing of research participants
- Facilitate high-quality health research to the public benefit
- Be proportionate, efficient and coordinated
- Maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency.

The report contains 17 recommendations for a new regulation and governance pathway. The recommendations in the report were intended to 'deliver a level of change that would substantially improve the regulation and governance pathway as well as the culture within which it operates for the good of patients, the public and the economy'. The recommendations were designed to improve the UK environment for health research and streamline regulation and governance, without undermining its effectiveness. A summary of the main themes identified, and the associated recommendations are provided in Table 8.

## Vision for the governance framework

The report's vision for regulation and governance incorporated the traditional functions of a regulator (in terms of setting, monitoring and enforcing standards) with a desire to improve the regulatory and governance environment for patients and researchers. The objectives of the governance framework were:

- Protect participants' safety and promote highquality health research
- Apply regulatory and governance requirements in a way that is proportionate to the potential benefits and harms of the research
- Raise research standards with an emphasis on promoting compliance rather than simply policing non-compliance
- Clearly define the roles and responsibilities of the various stakeholders
- Have the authority and expertise to provide patients, clinicians, researchers and the general public with clear guidance and advice
- Be consistent (including across the UK) transparent and accountable
- Be independent of government
- Provide a single point of entry and exit for research applications and enable all checks and approvals to be undertaken without duplication or unnecessary delay
- Facilitate the UK's viability and attractiveness as a site for clinical trials through ambitious and internationally competitive timeframes by which all regulatory and governance assessments must be completed.

The strategy for implementing the recommendations of the Rawlins Review considered individual recommendations to be implemented as a 'whole', (inclusive of a regulation and governance framework) through the establishment of the Health Research Authority (HRA). The HRA was viewed as the most efficient and effective way to deliver the required improvements by providing coordination and oversight across the whole regulation and governance pathway in the UK.

## Regulation and governance of clinical trials: five years on

In 2016, a joint workshop was again convened by the Academy of Medical Sciences along with Cancer Research UK and the Wellcome Trust to review and discuss what progress had been made towards implementing the recommendations contained in the academy's 2011 report *A new pathway for the regulation and governance of health research*. The workshop aimed to highlight areas where improvement was still needed and identify any issues that may have arisen since 2010.[121]

It was agreed that the establishment of the HRA and the centralised HRA approval process had improved the simplification and coordination of NHS research governance and reduced timelines for NHS permissions and study set-up. Key successes were noted as well as the remaining challenges which include the need to:

- Embed a research culture within the NHS, building on the progress made in improving research delivery timelines
- Improve the regulation and governance of health research which is needed to enable the UK to compete at an international level, especially in light of the UK leaving the EU. The importance of the UK maintaining harmonisation with the EU system was agreed including continued access to the EU portal and database for clinical trials, while considering opportunities for more flexibility in some areas of regulation such as for singlestate trials
- Adopt a whole-of-system approach to the regulation and governance of health research with metrics that captured the whole pathway to facilitate and support competitive UK research
- Address the disconnection between those making high-level decisions on how regulations should be applied and those implementing them on the ground. The disconnection leads to decision-making that is overly rigid, disproportionate and risk averse

- Establish systematic routes for patient input into the development and function of regulatory structures, particularly around the collection, use and sharing of patient data for health research
- Develop regulations pertaining to patient data for health research including issues of data protection, duty of confidentiality and NHS data governance, and relating to data security and opt-out consent for the use of identifiable patient data (as an outcome of the two reviews conducted by Dame Fiona Caldicott, the National Data Guardian). [122,123]

The grey literature search revealed several UK policy documents that have relevance to health research or clinical trials. Details of these documents are summarised in Table 9, Appendix 1.

## Regulatory culture and research governance

Research regulation and governance is widely considered to be essential to protect human subjects from undue harm. However, as highlighted in many of the reports outlined above, health research governance has been the subject of considerable debate and discussion across the globe. Most specifically, concern was raised about the overly complicated, bureaucratic and duplicative review processes for the approval of health research, including clinical trials.

In order to understand why duplication in health research regulation was occurring in the UK and what impact regulation was having on health research governance, the Policy Research Programme in the UK Department of Health commissioned an independent report. The report was conducted by RAND Europe (a notfor-profit research institute) and the findings published in 2013.[124]

The study sought to find answers to the following research questions:

- What is the impact of regulation on research governance and specifically in relation to the behaviour of the regulated sector (including applicants, sponsors, research institutions and NHS trusts)?
- 2. What can be learned from a comparative study of the practice of those who are subject to regulatory requirements across sectors and countries?

The study design was a comparative study of the review of health research systems in Australia, Brazil, Canada, China, India, Russia and the USA. The study also involved a comparison of the health research sector with the practices of other sectors that are subject to regulatory requirements: the medical drug approval, environmental risk regulation and financial sectors.

Findings concluded that the health research systems of the seven countries included in the cross-country comparison used different models to regulate and review research, although most had dual components of both decentralised (local) and centralised (national) processes. For trials involving more than one site or jurisdiction, there had been calls from researchers and sponsors to centralise and streamline review processes; however, institutions feared that the loss of local oversight would mean less control over the nature and conduct of clinical trials. Moreover, there were concerns about liability and responsibility. Nonetheless, several countries including Australia, Canada and the United States of America (USA) had introduced or proposed mechanisms to ameliorate the way the regulatory processes were perceived by stakeholders including:

- Developing accreditation systems to instil trust into review boards which receive decisions from other review boards
- Certifying staff (such as through a national training program) to provide the required mutual trust in the decision-making of others
- Encouraging reciprocal agreements to accept other's decisions
- Increasing the transparency of the decisionmaking process to build trust
- Increasing interaction and communication between committees to establish relationships and trust between the individuals involved
- Providing education and encouraging the use of evidence to understand the relative risk compared to the hypothetical risk
- Evaluating or auditing the current system to determine overall success – thereby producing more confidence in the system.

While the authors of the study acknowledged the challenges of research governance were not unique to any country, the mechanisms to address these challenges varied in success. Suggested solutions for implementation included:

- Clearly establishing and articulating the roles and authority of ethics committees. In particular, establishing an understanding of the various actors' legal liabilities (i.e. ethics committee, institution, sponsor)
- Establishing national standards or guidance for this training provided by the Association for the Accreditation of Human Research Protection Programs (or a similar entity)
- Implementing agreements to establish trust and confidence in other committees' decisions such as the Canadian Reciprocal REB review and MOUs signed between states in Australia
- Considering whether sequential or stepwise processes could reduce duplication of review. Sequential HREC and SSA approvals allow each person to be assured of the approval before them. In the UK SSA occurs simultaneously with overall review by the centralised National Research Ethics Service (NRES)
- Using standard operating procedures to reduce duplication by reducing uncertainty in the decisions of others. A standard set of criteria to all reviews creates confidence that others have applied the same rigorous process to approval
- Establishing strict timelines for sign off projects.

The cross-country comparative analysis (across seven health research systems and three additional regulated sectors – medical drugs, environmental management and the financial sector) focused on three key questions:

- Are there common elements or initiatives across the sectors which have affected the way in which the regulation or regulatory system is received and responded to by stakeholders?
- 2. How has the practice of those subject to regulation been affected by those elements and in what ways?
- 3. Can any lessons be extrapolated for the research governance in the UK?

The study found that although specific regulatory mechanisms varied within each sector there were common themes identified across sectors that could be explored further for their applicability to research governance including:

- Increased provision of educational initiatives to improve awareness and training among actors
- Increased transparency and promotion of a culture of openness between researchers, sponsors, trusts, institutions, and the public as to the decision-making and approval processes that are followed
- Development of additional mechanisms to foster trust within the system. Formal (accreditation schemes or memoranda of understanding) and informal (networking, relationship building) mechanisms should be considered
- Consideration of the regulatory structure and where trade-offs may need to be made to align regulatory philosophies and objectives
- The use of incentives (in particular the role of the public in creating a demand for research) should be explored. This includes determination of different indicators and metrics against which actors can be evaluated, for example, research publications, trials hosted and number of new participants recruited.

The main objective of the UK Government is to make clinical research 'faster and easier'. To achieve this objective the NHS, through the NIHR, HRA and other agencies, has introduced several key measures that address many of the frequently cited impediments to conducting clinical trials such as:

- Simplifying and streamlining administrative and regulatory procedures to improve the initiation and delivery of clinical trials by working with the HRA to simplify approval processes for ethical research, including implementing an HRA unified approval process for research in the NHS
- Providing access to clinical trial expertise and collaborations as well as designated funding and infrastructure for the life sciences industry, coordinated through the NIHR Office for Clinical Research Infrastructure and Clinical Research Network

- Integration of all current academic training and higher career personal awards into a new academic structure. The NIHR Academy will host all academic training and career development activity. Once fully established, the NIHR Academy will ensure that the current and future needs of the wider research community and other key stakeholders are met, and are aligned and integrated with Department of Health and NHS strategies [125]
- Monitoring and managing individual NHS providers' performance in commencing and delivering research and making it accountable and transparent through changes to new NIHR contracts. NHS trusts with new NIHR contracts report their own site-level performance which includes, for clinical trials, a 70-day benchmark to recruit first patients. Performance is linked to funding. A minimum data set has also been developed for HRA approval processes (NIHR minimum data set v5.0 – 23 March 2017)<sup>39</sup>
- Each year, a Research Activity League Table is published by the NIHR-CRN which details and benchmarks research activity across all NHS trusts in England. The table provides a picture of how much clinical research is happening, where, in what types of trusts, and involving how many patients
- Metrics are also used to monitor the performance of the NIHR Clinical Research Network as a whole. The CRN reports on initiation and delivery, at network level, of all research within the NIHR portfolio
- Streamlined human resources arrangements through the implementation of the Research in the NHS: Human Resource Good Practice Resource Pack. The resource pack comprises two elements. Firstly, the Research Passport System for issuing honorary research contracts or letters of access. The research passport provides evidence of pre-engagement checks undertaken on the researcher in line with NHS employment check standards. Secondly, NHS to NHS arrangements for sharing and accepting pre-engagement checks between NHS organisations when NHS staff want to undertake research within the NHS outside of their employing trust
- Providing support to help the NHS improve performance, through the NIHR Research Support Services framework and associated tools, standard operating procedures and other associated information

- Leadership Support and Development for research and development Managers and Directors through the NIHR Leadership Support and Development program
- Champions for Research Support who are hosted by the HRA and whose role is to disseminate messages throughout the NHS and act as advocates for effective research management and delivery
- Nationally approved standard research agreements and standard operating procedures.<sup>40</sup>

The NHS rationale for the implementation of the above initiatives is based on experience suggesting that clinical research in the NHS could be made faster and easier if the board, researchers and managers work in partnership in a clear integrated approach to research. Organisations then develop a research culture that understands and promotes the benefits of research (both pragmatic and proportionate to risk) to patients. They become proactive in planning and managing research studies throughout their life cycle, refocusing research and development office staff from permission to delivery. Responsibilities and activities shift to monitoring performance including boardlevel KPIs and taking action where appropriate, marshalling public demands for opportunities to participate in research, pooling research nurses and developing lists of research-ready patients.<sup>41</sup> Figure 6 provides an overview of the legislation, policies and guiding frameworks, and the organisations responsible for the oversight and conduct of clinical trials in the UK.







#### The National Institute for Health Research (NIHR)

The NIHR<sup>42</sup> was created in April 2006 under the 2005 UK Government strategy for health research, *Best Research for Best Health*, with the aim of transforming research in the NHS.[126] The NIHR is funded through the Department of Health and is the research arm of the NHS. It is a large, multi-faceted and nationally 'virtual' organisation and its remit is to improve the health and wealth of the nation through research. The objectives of the NIHR are to:

- Establish the NHS as an internationally recognised centre of research excellence
- Attract, develop and retain the best research professionals to conduct people-based research
- Commission research focused on improving health and social care
- Strengthen and streamline systems for research management and governance
- Increase the opportunities for patients and the public to participate in and benefit from research

- Promote and protect the interests of patients and the public in health research
- Drive faster translation of scientific discoveries into tangible benefits for patients
- Maximise the research potential of the NHS to contribute to the economic growth of the country through the life sciences industry
- Act as a sound custodian of public money for the public good.

The NIHR works in partnership with many sectors including the public and service users, the NHS, public health, other government funders, the academic sector and industry. The NIHR manages its health research activities through four main work strands:

**Infrastructure**: providing the facilities and people for a thriving research environment including funding a range of infrastructure facilities such as biomedical research centres, clinical research facilities for experimental medicines, and translational research collaboration in dementia and rare diseases.

**Faculty**: supporting the individuals carrying out and participating in research through research training and career development programs and individual schemes to support the academic training paths of all health professionals involved in research.

**Research**: commissioning and funding research. This includes a comprehensive range of funding for research programs, the provision of funding for three national research schools, and support for the Surgical Reconstruction and Microbiology Research Centre. The NIHR provides several research review services – the UK Cochrane Centre and Review Groups, the NIHR Dissemination Centre, the Technology Assessment Reviews, and the Horizon Scanning Research and Intelligence Centre.

Patients and their families and carers are regarded as key partners in the NHS mission to improve the health and wealth of the nation. In 1996, the NIHR established INVOLVE to actively support public involvement in NHS, public health and social care research. INVOLVE is a national advisory group and its role is to bring together expertise, insight and experience in the field of public involvement in research, with the aim of 'advancing it as an essential part of the process by which research is identified, prioritised, designed, conducted and disseminated'.<sup>43</sup> In 2018 the NIHR released the *National Standards for Public Involvement in Research*. The national standards provide a framework for reflecting on and improving the purpose, quality and consistency of public involvement in research. The aim of the standards was to provide clear, concise benchmarks for effective public involvement alongside indicators against which improvement can be monitored.[127]

**Systems**: promoting faster, easier clinical research through unified, streamlined and simple systems for managing ethical research and its outputs. There are three components to this initiative:

- Ensure NHS providers' performance in starting and delivering research is transparent and accountable through the NIHR contracts including the introduction of the 40-day benchmark for initiation of research
- Provide support to help the NHS improve performance. This includes the NIHR Research Support Service Framework comprising a set of tools and guidelines that enable providers, particularly research managers, to take a consistent, streamlined and risk-proportionate approach to considering their participation in research. The NIHR coordinated system for gaining NHS permission is a single study-wide view to consider compliance issues allowing local reviews to focus on whether individual sites can deliver a study
- Work with the HRA to simplify approval processes for ethical research by, for example, supporting a smooth implementation of HRA approval.

The NIHR also provides and supports research information systems and intelligence initiatives to speed up the research process and maximise the use of information collected in routine NHS care. For example, Clinical Practice Research Datalink, which is a partnership between the Medicines and Healthcare Products Regulatory Agency and the NIHR, was established to provide a safe and secure access point to patient electronic health records that are collected routinely by the NHS to support research. Researchfish is a national assessment tool to capture the progress of commissioned research on an annual basis and provide the NIHR with insight into its funded activities. The aim is to capture and demonstrate the value and impact of the research which the NHS funds.

#### **Health Research Authority**

The Health Research Authority (HRA)<sup>44</sup> was established by the UK Government as a nondepartmental public body in 2015 through the Health Care Act 2014, to give it greater independence and stability than it previously had as a special health authority. The role of the HRA is to protect and promote the interests of potential research participants and the general public in both health and social care research. The HRA has several core responsibilities including: The National Research Ethics Service which comprises research ethics committees and the Integrated Research Application System.

HRA approval is the unified approval process for all project-based research in the NHS in England. The unified approach was fully implemented in 2016. The HRA approval system brings together the assessment of governance and legal compliance, which is undertaken by dedicated HRA staff with the independent ethical opinion provided through the UK Research Ethics Service thereby enabling the submission of only one application. This process replaces the need for local checks of legal compliance and related matters by each participating organisation in England, thereby enabling participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.

HRA approval applies only to the NHS in England. Studies with sites in Northern Ireland, Scotland or Wales are supported through existing UK-wide compatibility systems, by which each country accepts the centralised assurances, as far as they apply to national coordinating functions.<sup>45</sup>

In addition to its coordinating functions, the Integrated Research Application System is a centralised, online application system that streamlines the process for applying for permissions and approvals to conduct health and social care research in the UK by reducing duplication and making it simpler and less timeconsuming. The Central Booking Service is a telephone booking service for applications for HRA approval and for research ethics committee only review.

#### The National Institutes of Health (NIHR) Clinical Research Network (CRN)

The CRN<sup>46</sup> is made up of 15 local clinical research networks that cover the length and breadth of England. The CRN delivers research across 30 clinical specialties at a national and local level. The NIHR-CRN's remit is to support the delivery of high-quality clinical research in the NHS and provide support for the initiation and delivery of funded research in the NHS. The NIHR-CRN is embedded within the NHS and comprises local NHS staff and other support funded via Department of Health agreements with NHS trusts acting as local clinical research network (LCRN) hosts. The NIHR-CRN is the English component of the UK Clinical Research Network (UKCRN) developed under the auspices of the UK clinical research collaboration.

The CRN's structure includes the National Coordinating Centre (CRNCC). The CRNCC enables the CRN to support around 5,000 clinical research studies each year, which is referred to as the CRN portfolio. The CRN meets the costs of NHS staff that support research and it provides specialist training. The CRN also meets the costs of NHS facilities (such as scanners and x-rays) that are required to conduct the study. In this way the research is not subsidised with funding that has been provided for patient care. The CRN also provides resources to manage performance and data submissions, facilitates training, assists to identify and recruit patients and a range of activities across the trial sites. The 15 CRNs provide on-the-ground infrastructure to assist with delivery and recruitment for studies. Those clinical research (non-commercial) studies that meet the specified eligibility criteria are added on to the CRN portfolio of studies and are able to receive study support from the CRN.

#### UK registered clinical trials units

The UK registered clinical trials units (CTUs)<sup>47</sup> are specialist units that have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. To improve the quality and quantity of available expertise to carry out clinical trials in the UK, a registration system has been established for clinical trials units responsible for coordinating multi-centre clinical studies. To gain UK registration, CTUs must demonstrate: a track record of experience in coordinating multi-centre trials, expert staff to develop studies, robust quality assurance systems, and evidence of longterm viability of capacity for trials coordination.

#### **UK Clinical Trials Collaboration (UKCRC)**

The UKCRC<sup>48</sup> was established in 2004 with the aim of re-engineering the clinical research environment in the UK. The UKCRC brings together several stakeholders including the NHS, research funders, industry, regulatory bodies, royal colleges, patient groups and academia to facilitate and promote research and training across the UK.

#### **UK Clinical Trials Gateway**

The UK Clinical Trials Gateway<sup>49,50</sup> is an online facility that enables potential trial volunteers to search for clinical trials from two main sources: the US-based <u>ClinicalTrials.gov</u> register and the UK-based <u>ISRCTN</u> register.

#### Legislation

Section 13L of the Health and Social Care Act 2012 places a statutory duty to promote research, and powers to support it, on the Secretary of State and on all levels of the NHS including NHS England and clinical commissioning groups. The NIHR provides a key means through which the Secretary of State discharges this duty.<sup>51</sup> This was updated to the Care Act 2014. The NHS Constitution highlights the UK's 'commitment to innovation and to the promotion, conduct and use of research to improve the current and future health and care of the population'.52 Other key policy documents: Next Steps on the Five Year Forward View [128] and the Life Sciences Industrial Strategy [129] confirmed NHS England's commitment to creating a more fertile environment for clinical trials and articulated a vision to further improve UK clinical trials capabilities.

#### Policy framework for clinical trials

The primary framework for clinical trials is the *UK Policy Framework for Health and Social Care Research* v3.2 2017.[20] The policy framework was developed in partnership between the four UK Health Departments and the HRA. It applies to England, Northern Ireland, Scotland and Wales. In accordance with section 111 (6) and (7) of the Care Act 2014, the document provides statutory guidance to which local authorities, NHS trusts and NHS foundation trusts in England must have regard.

The purpose of the UK Policy Framework for Health and Social Care Research is to set out principles of good practice in the management and conduct of health and social care research that take account of legal requirements and other standards. These principles serve to:

protect and promote the interests of patients, service users and the public in health and social care research by describing ethical conduct and proportionate, assurance-based management of health and social care research so as to support and facilitate high-quality research in the UK that has the confidence of patients, service users and the public.

The policy framework sets out principles and responsibilities at a high level that take into account relevant legislation in the UK. The aim is to ensure a consistent approach to coordinating and standardising regulatory practice to achieve compatibility across the UK for the management and conduct of health and social care research.

The framework applies to health and social care research that is within the responsibility of the HRA or the devolved administrations' health departments. This includes research undertaken in or by a UK health department, its non-departmental public bodies or the NHS and social care providers; clinical and non-clinical research undertaken by NHS or social care staff using the resources of health and social care providers; and any research undertaken within the health and social care systems that might have an impact on the quality of those services.

# Implementation of the policy framework

The implementation of the framework is supported by national operational policies and guidance, standard operating procedures and operational platforms. Individuals and organisations with responsibilities under the framework are expected to adopt the operational provisions wherever relevant and are not to design their own. The principles and responsibilities outlined in the framework are reflected in the organisation's policies, procedures and practices.

## The national policy framework for clinical trials

The policy framework reflects the relevant legislation in the UK and takes account, where relevant, of the application of this legislation in each UK country while supporting UK-wide compatibility and consistency. The policy framework replaces the research governance frameworks previously issued in each of the four UK countries in accordance with the Care Act 2014 and with the agreement of the devolved administrations. Although the responsibilities for health and social care services have been devolved to the administrations in Northern Ireland, Scotland and Wales, these four UK health departments are committed to maintaining compatible standards for research ethics, management and conduct across the UK. Otherwise, cross-border research could be undermined by incompatible expectations between England, Northern Ireland, Scotland and Wales.

## The local policy framework for clinical trials

The local policy framework outlines the responsibilities and accountabilities of both individuals and organisations involved in research at a high level. This includes chief investigators, research teams, funders, sponsors, contract research organisations, research sites, regulators of professions, other regulators, employers, and health and social care providers. At the local level, the framework documents the relationship between principles of good practice in the management and conduct of health and social care and the responsibilities of individuals and organisations.

#### Research Support Services Framework

Under the 2011 UK Government's *Plan for Growth* [130], a new health research regulatory agency, Research Support Services, was launched to 'facilitate consistent local research management and greatly improve performance'. The plan for growth provided the framework for several initiatives designed to streamline regulation and improve the cost effectiveness of clinical trials. These included:

- Making future NIHR funding to providers of NHS services conditional on meeting benchmarks, including a 70-day benchmark to recruit first patients for trials
- Making performance in the initiation and delivery of health research transparent and accountable and routinely enabling comparisons of research sites with one another, and against international benchmarks
- Requiring providers of NHS services, as a condition of NIHR funding, to play their part in a national system of research governance and provide timely and professional delivery of clinical trials
- Creating a health research regulatory agency at the national level to combine and streamline the approvals for health research.

At the local level, the government provided incentives for efficiency in research initiation and delivery through a framework of good practice and standard procedures called the NIHR Research Support Services to facilitate consistent local research management and greatly improve performance. NHS trusts that adopted the framework had access to NIHR financial support for these activities. For clinical trials, the NIHR (from 2012) published outcomes against public NIHR benchmarks, including an initial benchmark of 70 days or less from the time a provider receives a valid research protocol to the time when that provider recruits the first patient for that study.

In addition, the NIHR-CRN worked with trusts implementing the NIHR research support services and other partners to embed the practice identified in the NIHR-CRN North West Exemplar Program. This program demonstrated that, even with excessively complex research regulation, the UK was capable of delivering clinical trial set-up times to rival the best in Europe. This reflected the commitment of trust chief executives to research within their organisations, rapid escalation and prompt management of extraordinary issues, and executive oversight of performance metrics. The NIHR adopted the Research Support Services Framework for local health research management in 2011 to enable front-line staff to collaborate in offering consistent, professional streamlined services to support clinical research in the NHS in England. The NIHR expected NHS organisations to demonstrate that they are using the Research Support Services Framework when undertaking NIHR-adopted research studies (NIHR portfolio studies), and applying the same principles to non-portfolio studies, to promote uniformity and consistency of practice. The Research Support Services Framework applied to all types of research in the NHS.

#### **Roles and responsibilities**

The roles and responsibilities of key proponents of clinical trials are underpinned by the rationale that:

- Health research and development is core business for the NHS and is a core element of the NHS Operating Framework
- Research and development across the NHS is central to the UK's international reputation as a leader in life sciences
- The role of the 'research manager' in an organisation is multi-faceted and is typically the person with delegated responsibility for ensuring that the NHS fulfils its regulatory requirements as an autonomous legal entity. They also work alongside the responsible senior investigator to facilitate the local management of the study and protect the integrity of the study on the site. In some cases, they have to manage potential conflicts of interest between this support role and their role in assuring compliance with good governance
- The research manager and research and development office are often the person/ team acting on behalf of the organisation in matters relating to research and development management
- The Research Support Services Framework does not specify 'who' undertakes specific roles (trust, NIHR, CRN etc.) but identifies those activities for which the organisation is accountable.

#### Purpose of the Research Support Services Framework

The purpose of the Research Support Services Framework is to support proportionate management and governance of research and development studies, and to:

- Provide a consistent framework for research managers and other stakeholders
- Provide standard operating procedure guidelines for NHS organisations wanting to participate as a host research site (as a participating organisation) and for NHS organisations intending to sponsor a study
- Provide guidelines for NHS organisations to develop a set of consistent and streamlined standard operating procedures for all types of studies, including clinical trials. It also describes specific tools used by these SOPs including the research and development Operational Capability Statement and the study planning tools
- Ensure standard operating procedures are to be used to manage operational risks in a way that is proportionate to study risks
- Provide standard operating procedures that are intended to be applicable to all NHS organisations and used by research managers and staff within the research and development office in NHS organisations. This includes those individuals involved as sponsoring or participating organisations delivering clinical trials

The standard operating procedures are intended to cover the processes associated with the research and development lifecycle of typical studies. The processes or stages include:

- trust research and development readiness
- study development
- readiness assessment
- study preparation
- study confirmation
- study start-deliver
- study assurance
- study closure.

The NIHR standard operating procedure dependency frameworks align with the Coordinated System for NHS Permission (CSP) and its implementation using the Research and Development Management Information System.

The Research Support Services Framework contains standard operating procedure templates, the research and development operational capability statement, participating organisation guideline documents and sponsoring organisation guideline documents.

## Research and development operational capability statement

The NIHR expects that organisations will use and maintain a research and development operational capability statement which is a board-approved statement of agreed research and development operating principles (as part of the organisation's research and development readiness). This statement provides information about the organisation's commitment to health research and development, and the roles and responsibilities of the different stakeholders in the organisation in delivering these commitments. The statement is prepared by the research manager in agreement with other stakeholders such as service managers (for pathology, radiology etc.) and owned by the organisation's board. The statement puts research and development on the agenda of the board, raising the profile of the research and development office in managing operational risks on behalf of the organisation. It also provides a mechanism for reporting progress (e.g. as part of quality accounts reporting) and escalating any research and development governance decision or issue that cannot be addressed through normal business practice.

The statement names key people who are authorised to make decisions on behalf of the organisation and describes the responsibilities delegated to them. It also provides the framework within which the research manager is empowered to make governance decisions on behalf of the organisation (when working with investigators, sponsors etc.). It supports the research manager in getting timely support from other stakeholders in making these decisions (e.g. when progressing NHS permission for a study or when making a decision to sponsor a study). The statement is particularly important in supporting the early and rapid assessment of operational risks at the start of the NHS permission process for a new study or when making a sponsoring decision.

The statement contains information on the following areas:

- Organisation research and development management arrangements
- Organisation study capabilities
- Organisation services
- Organisation research and development interests
- Organisation research and development planning and investment
- Organisation research and development SOP register
- Planned and actual studies register
- Other information which may be relevant to the organisation when making research and development governance decisions.

In summary, the UK has implemented a governance framework for clinical trials and health research. The governance framework comprises a number of interlocking elements including a centralised and streamlined ethicsapproval process; a suite of resources and services designed to support and facilitate research at the local level; metrics to measure and benchmark performance that is tied to funding arrangements; and clearly articulated roles and responsibilities at all levels of the healthcare system. Significant government investment in research and development, and establishing designated departments and agencies to oversee and support health research across the UK, have been key enabling factors in the improvements seen in the level of health research and clinical trial activity. Most importantly, considerable effort has been made in the UK to bridge the research/clinical practice gap and embed research as a core component of health service delivery.

### South Korea (Republic of South Korea)

South Korea is a densely populated country, with a population of 50.2 million people and 25% of the population concentrated in the Seoul metropolitan area. The average life expectancy at birth is 82.1 years (2015). Health care is provided through a centralised healthcare system funded by a national health insurance that covers 98% of the population. There are 3,600 hospitals (major university hospitals which provide more than 1,000 beds), 43 teaching hospitals, 60,000 clinics and 93,000 practising clinicians.<sup>53</sup> The pharmaceutical industry in South Korea is one of the largest in Asia with an estimated worth of A\$17 billion, with expected growth to reach A\$24.3 billion by 2020.<sup>54</sup>

Traditionally, industry-sponsored clinical trials have been conducted in North America, Western Europe and Oceania. In recent years there has been an increase in the globalisation of clinical trials conducted by the pharmaceutical industry and rapid expansion into Asia, Central and Eastern Europe, and South America. This shift was driven by commercial trial sponsors to reduce operational costs and ensure the timely recruitment of large patient populations. In response, the South Korean Government invested in initiatives to improve competitiveness, attractiveness and market share: establishment of contract research organisations to focus on securing global clinical trials; streamlining regulatory requirements and the harmonisation of guidelines for clinical practice and research.[131]

South Korea actively markets itself as one of the top global competitors and a hub for world-class clinical research and is ranked among the top 10 countries in the world for the number of clinical studies conducted annually. South Korea was ranked sixth in the world in 2017 (up from eighth place in 2016) with 3.5% market share behind the USA (24.5%), Germany (5.3%), UK (5%), Canada (3.9%) and China (3.7%).[132,133–136]<sup>55</sup>

# Government support for the pharmaceutical clinical trials industry

The South Korean Government considers the pharmaceutical industry and the clinical trials sector as being integral to the country's economic success. This is reflected in the proportion of gross domestic product (GDP) which South Korea spends on research and development. According to the UNESCO Institute for Statistics, South Korea spends 4.3% (78.2% of business sector) of GDP which ranks it as the leading country on research and development spending.<sup>56</sup> In comparison, Australia is ranked 14th with 2.2% of GDP spent on research and development. In addition to fiscal support, the government's policy development for expansion of the pharmaceutical industry has been substantial and facilitated the shift to early phase clinical trials (Table 6).

This includes the Framework Plan for Biotechnology Promotion (1994), the 2012 Pharmaceutical Industry Competitiveness Enhancement Plan (2012) and the Pharma South Korea 2020 Roadmap to stimulate innovative drug development and overseas expansion of South Korean pharmaceutical companies. The government provides tax deductions for research and development costs and has established the Global Pharmaceutical Industry Development Fund through the Ministry of Health and Welfare, the Pharmaceutical Industry Project Fund through the South Korea Financial Corporation and the Pharma Corporate Partnership Fund through the National Pension Service.<sup>57</sup> Investment by the South Korean pharmaceutical industry has also been considerable with total investment of over US\$2.6 billion to 2014 to build a pharmaceutical production infrastructure that conforms to USA current good manufacturing practice regulatory standards. In 2014, South Korea's pharmaceutical market was estimated to be worth approximately US\$17 billion (2014), with US\$2.1 billion in exports.58

There have been several major government sponsored initiatives for clinical trials, including the establishment of the South Korean National Enterprise for Clinical Trials (KoNECT); The KoNECT Collaboration Center; Regional Clinical Trial Centres; Global Clinical Trial Centers of Excellence, and identified and designated research-driven hospitals. Historically, the major focus for South Korean clinical trials has been Phase III clinical trials; however, this focus has now shifted to earlier phase trials.

Table 6: Overview of South Korean Government and industry organisation initiatives for clinical trials

Year	Organisation/initiative
1945	South Korea Pharmaceutical Manufacturer's Association
1987	South Korean Drug Development Fund
1994	Introduction of the framework for biotechnology promotion
1995	South Korea implements Good Clinical Practice – GCP guidelines (KGCP) and becomes the 2nd country in Asia to implement GCP
1999	Establishment of the South Korean Health Industry Development Institute (KHIDI) to expand healthcare research and development investment and competitiveness
1999	South Korean Research-based Pharmaceutical Association
2001	Revision of KGCP to be equivalent to International Conference on Harmonisation and Good Clinical Practice
2002	Separation and introduction of IND from NDA system which reduces IND approval timeframe to 30 days
2002	Establishment of Clinical Trial Authorisation Process
2002	South Korean Association of Institutional Review Boards
2004	Establishment of the first clinical trial center in South Korea
2007	Establishment of KoNECT
2010	South Korean Clinical Research Information Service
2011	South Korean Drug Development Fund
2012	Release of the 2012 Pharmaceutical Industry Competitiveness Plan
2012	Pharma South Korea 2020 Roadmap (designed to stimulate innovative drug development and overseas expansion of South Korean pharmaceutical companies)
2012	Establishment of new Global Centers of Excellence for Clinical Trials
2013	South Korean Food and Drug Administration renamed to Ministry of Food and Drug Services
2015	Establishment of the KoNECT Collaboration Center

## Key clinical trial organisations in South Korea

#### South Korea Health Industry Development Institute

The South Korea Health Industry Development Institute<sup>59</sup> is a government-funded institution established in 1999 under the South Korea Health Industry Development Institution Act as the primary vehicle for the overall administration of the national health industry. The South Korea Health Industry Development Institute provides a suite of services under four domains of responsibility: policy development and information sharing; reinforcing the capability of the health industry; health and medical service technology research and development support; and government project experience. The South Korea Health Industry Development Institute has also established six global business offices to facilitate the promotion and expansion of the South Korean health industry and establish networks with local government agencies.

## South Korea Association of Institutional Review Boards

South Korean Association of Institutional Review Boards was founded in 2002 to promote ethical oversight for scientific and socially responsible clinical research through adherence to South Korean Good Clinical Practice and guidelines. It also provides training, education and workshops to improve healthcare professionals' research ethics capabilities and understanding throughout the country.

## South Korea National Enterprise for Clinical Trials

KoNECT<sup>60</sup> was established in 2007 by the South Korean Ministry of Health and Welfare as a government-funded, non-profit organisation responsible for fostering clinical research in the Republic of South Korea.[137] In 2014, KoNECT was transformed into a foundation to continue its efforts to develop the necessary infrastructure and provide support for sponsors interested in conducting clinical trials in South Korea. KoNECT's primary objectives are to:

- Develop the nation's clinical trial infrastructure
- Train and support clinical trial professionals
- Provide relevant clinical trial-related information and analysis
- Promote the country's advanced capabilities while working closely with domestic and international partners.

#### The KoNECT Collaboration Center

The KoNECT Collaboration Center<sup>61</sup> is a 'onestop shop' for clinical trial planning aimed at accelerating the smooth and efficient conduct of clinical trials in South Korea, and promoting and facilitating global networking, collaboration, innovation and business partnering in clinical research. The collaboration centre was established in 2015 with the support of the South Korean Government under the auspices of KoNECT. The major services and features of the KONECT Collaboration Center include:

- KIIS (KoNECT Integrated Clinical Trial Information System)
- One-stop shop for clinical trial planning (including matching with recommended partners)
- Business centre and administrative support
- South Korean Clinical Trial Interactive Gallery
- Liaison with clinical trial networks.

#### KoNECT Integrated Clinical Trial Information System

KoNECT Integrated Clinical Trial Information System (KIIS)<sup>62</sup> is an integrated online database that is a repository of information about South Korea's clinical trial industry and a centralised information resource for companies and sponsors. KIIS is a one-stop shop for information about South Korea's clinical trial industry. Information on the KIIS website is structured under the following domains:

#### Industry overview

Industry overview provides facts and figures regarding South Korea's macroeconomic indicators, including datasets for the healthcare, pharmaceutical and clinical trial industries.

Healthcare industry

- General indicators of health status
- Healthcare resources
- Healthcare expenditure.

Pharmaceutical industry

- South Korean pharmaceutical market
- Medicines and medical supplies
- Pharmaceutical companies
- Research and development for medicine and medical supplies.

#### Clinical trials industry

- Number of approved trials
- Number of approved trials by phases
- Number of approvals by clinical trial authorisation holders
- Number of clinical trial authorisation approvals by therapeutic areas
- New drug approvals by biopharmaceuticals
- New drugs approvals.

## Single access point to South Korea clinical trials

The aim of the national platform is to provide a single access point for patients, families, healthcare professionals, researchers and the public to search, identify and access information about registered clinical trials in South Korea. The database uses information derived from two clinical trial registries:

- 1. Clinicaltrials.gov
- 2. World Health Organization ICTRP (International Clinical Trials Registry Platform).

These two registries incorporate multiple other clinical trials registries internationally, such as EU Clinical Trials Register (EU-CTR) and Australian New Zealand Clinical Trials Registry (ANZCTR).

#### **Patient Data**

Patient Data is an epidemiology database of key diseases in South Korea. The epidemiological data covers incidence/prevalence rate, diagnosis, treatment, and risk factors. Sponsors/ researchers looking to conduct a clinical trial can use the database to identify, for example, the number of eligible patients, local medical practices and the relevance of eligibility criteria for trial protocols.

#### **Regulatory process overview**

Comprises flow diagrams and PDF guidelines for:

- Investigational new drug (IND) approval process
- New drug application (NDA) process
- Clinical trial materials.

#### **Treatment guidelines**

This section of the database provides treatment and diagnosis guidelines developed by South Korean medical societies or associations for specific therapeutic areas. Contents of the treatment and diagnosis guidelines are provided to suggest standards of care and improve the clinical decision-making process for clinicians and sponsors. Database is searchable by disease and PDF documents are available for download.

#### Site and investigator information

The data provided in the site/investigator database is voluntarily registered by clinical trial sites and investigators in South Korea. The site/ investigator database is primarily designed to enable sponsors to make an informed decision about site and investigator selection for clinical trial development in South Korea. An additional aim is to foster collaboration and networking among sites and investigators. Sponsors or researchers can search for either a clinical trial site or an investigator.

#### Site database

The site database can be searched by hospital type, location, type of study, number of studies conducted over past five years, mutual recognition among IRBs, electronic IRB submission system, international accreditation, inspection by foreign federal agency, audit by foreign sponsors.

#### Investigator database

This database enables sponsors to search for an investigator by qualifications, therapeutic focus/disease area, years in clinical practice, completion of GCP training, and experience in clinical studies (role, IST/CST, phase, status).

#### **KoNECT Partners**

The information in KoNECT Partners is voluntarily provided/registered by KoNECT partners and is primarily focused on local companies.

A partner is defined as any company related to non-clinical development and related fields of business, including but not limited to a contract research organisation, central laboratory, clinical logistics company, and other stakeholders in the pharmaceutical industry as a whole.

Information contained in the KoNECT Partner database includes number of employees, overseas presence, overseas network/alliance partner, KoNECT accreditation and service area.

#### Networks

Information relating to networks is voluntarily provided and/or registered by KoNECT networks. Eligible networks may be regional investigators' networks that investigate ethnic differences among Asian populations, that have research interests in diseases with high incidence or prevalence rate in Asia, or that are searching for global sponsors to propose translational researches, or clinical development plans.

KoNECT provides a range of supports for networks including:

- Organising networks' regular and ad hoc meetings, including forming advisory committees
- Participation in academic conferences and professional events
- Development of study protocols
- Small-scale researches.

## Clinical trial governance and regulatory agencies

The clinical trial governance and regulatory system in South Korea is organised as a highly centralised structure. There are two government departments that oversee and regulate clinical trials and pharmaceuticals in South Korea: the Ministry of Health and Welfare and the Ministry of Food and Drug Safety. In addition to KoNECT, the other relevant agencies associated with clinical trials and involved with the sector's funding, development and governance include the South Korea:

- Health Industry Development Institute
- Drug Development Fund
- Association of Institutional Review Boards
- Research Based Pharmaceutical Industry Association
- Pharmaceutical Manufacturers Association.

The government has established a coordinated system of clinical trial research infrastructure across South Korea. At the top of the hierarchical structure is the Global Centers of Excellence Program which is funded by the Ministry of Health and Welfare through the Clinical Trials Global Initiative. The Global Centers of Excellence Program supports five consortia, each with a focus on a specialised area such as complex clinical trials, biomedical technologies and studies in special populations for Phase I clinical trials. There are currently 22 clinical trial centres across South Korea, jointly government and hospital funded. Each clinical trial centre is affiliated with a university hospital. Clinical trial centres have been designed to provide world-class facilities and infrastructure, oversight of quality control, staff management and development.<sup>63</sup>

There are also approximately 170 clinical trial sites across the country which are inspected, accredited and certified by the South Korean Ministry of Food and Drug Safety.<sup>64</sup> An example of the Seoul National University Bundang Hospital Clinical Trials Center is provided below in Box 1.<sup>65</sup>

#### Box 1

#### Seoul National University Bundang Hospital Clinical Trials Center (SNUBH)

SNUBH is an academic clinical research center. It was designated as a Global Center of Excellence in Geriatric Early Clinical Trials (GREATS) by the Ministry of Health in 2012 and was the first pre-clinical and clinical molecular imaging centre in South Korea.

SNUBH at a glance:

- 1,381 beds; 6,000 outpatient visits per day
- 659 physicians
- 8 specialty clinic centres
- 21 staff and 254 investigators
- 4 IRB reviews per month
- 4 weeks from ethics submission to approval (full review).

Service areas:

- First in Human clinical trials
- Bioavailability and bioequivalence trials
- Pharmacometrics; modelling and simulation
- Phase II-IV
- Special population studies: elderly.

South Korea has attempted to address many of the governance issues detrimentally affecting clinical trials in developed countries.<sup>66</sup>

**Figure 7**: Overview of the South Korean approach to clinical research governance





## Initiatives to improve the quality of clinical trials

Initiatives to improve the quality of clinical trials include the following:

- Nationwide implementation of good clinical practice (GCP) training
- Designated funding for a training organisation (KoNECT) to develop and conduct education and training programs for clinical research associates, and health professionals
- Standardised training program in GCP for clinician researchers

- Government accreditation and oversight of designated clinical trial sites. Only institutions designated by the South Korean regulatory authority are permitted to engage in clinical trials
- IRBs/ECs at major sites accredited by international organisations including Forum for Ethical Review committees in the Asian and Western Pacific Region and Association for the Accreditation of Human Research Protection Programs
- Regular auditing of clinical research sites
- Establishment of global centres of excellence for clinical trials.

The Korean governance and regulatory agencies have implemented the following:

### Streamlined ethics and governance approval processes for faster study start-up times

- Streamlined clinical trial authorisation process enabling parallel institutional review board/ethics committee review and clinical trial authorisation review (time for entire process from submission of application to trial approval is four weeks)
- 30 working-day benchmark for clinical trial protocol approval
- 14 working days to review healthy volunteer studies
- IRB/ethics committee review (no local-site governance approval is required)
- Mutual recognition systems for ethical review processes
- Common ethical review application forms.

### Enhanced clinical trial infrastructure and operating environment

- Centralised healthcare system supported by near-universal national health insurance
- Network of clinical trial sites across the country
- Establishment of the South Korea Innovation Center for Global Clinical Trials, which is a one-stop service for global sponsors or partners to enter the South Korean market, and includes a consultation service for clinical trial site- selection and provision of virtual infrastructure
- Establishment of KoNECT.

#### Improved communication with patients, clinicians and international sponsors regarding the value and benefit of clinical trials

- Online, publicly accessible websites in two languages – South Korean and English
- Centralised, searchable online database of clinical trials
- Research culture embedded in the healthcare system with a research/clinical trial presence in most hospitals and medical centres
- Fostering of clinical trial partnerships with international sponsors.

#### Improved clinical trial coordination

- Designated government departments and organisations with responsibility for overseeing, coordinating, regulating and supporting clinical trials and the pharmaceutical industry
- Network of clinical trial centres of excellence, regional clinical trial centres and clinical trial sites.

#### Improved patient recruitment

 A single, online access point for patients, families, healthcare professionals, researchers and the public to search, identify and access information about registered clinical trials in South Korea.

### Clinical trial registration, reporting and metrics

The Clinical Research Information Service is an online registration system for clinical research developed in 2010 by the South Korean Centers for Disease Control and Prevention supported by the Ministry of Health and Welfare. The Clinical Research Information Service joined the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) in 2010 as a primary registry. The information registered in the Clinical Research Information Service is open to the public on a real-time basis, domestically and internationally. The Ministry of Health and Welfare requires registration of Ministry of Health and Welfare funded clinical research into the Clinical Research Information Service (which it designated as the public registry in 2012). The registration of other clinical research into a public registry system is not legally mandated in South Korea.[27]

It is unclear from information available in English how data is collected and reported, or how clinical trial performance (e.g. time to first patient recruited, length of time for ethics approval) is tied to funding or ongoing site accreditation.
#### Utilisation of e-health for clinical trials

- Standardised electronic clinical record form in major clinical trial centres which enables auto-migration of data into electronic health records
- Availability of the electronic medical record (EMR) and/or electronic health records for clinical trial feasibility assessment and data capture
- Clinical data retrieval systems that enable database-driven queries of anonymous EMR data and assessments of pool sizes of eligible patients meeting clinical trial inclusion/ exclusion criteria
- Pooling of anonymised patient data and establishment of investigator networks for defined therapeutic areas among institutions within each consortium.

In summary, the South Korean clinical trials governance system is centralised, highly structured, and organised with clear lines of responsibility for funding, regulation and accountability. It has the natural advantage of access to a large and ethnically diverse population with westernised disease patterns and clinical practices. South Korea has the advantage of centralised government, only one Ministry of Health and Welfare and significant government and pharmaceutical industry investment, which has enabled South Korea to establish an extensive and sophisticated infrastructure for conducting clinical trials. Some of the initiatives introduced by South Korea may be transferable to the Australian environment, for example, a centralised, online, publicly accessible database of clinical trials, standardised forms and templates for ethics review, and compulsory GCP education for research staff. However, Australia's complex health system and differing state and territory health structures, policies and guidelines pose barriers to establishing a centralised clinical trial governance framework such as that operating in South Korea.

### **Australia**

Australia has a population of approximately 24 million people. There are approximately 1,345 hospitals nationally servicing roughly 9.3 million total hospitalisations per year at an estimated cost of \$140.2 billion or 9.5% of GDP. While some private hospitals undertake clinical trials, most are undertaken in public hospitals, universities and research institutes.

Clinical trials are initiated by commercial sponsors representing multinational organisations such as pharmaceutical companies, smaller Australian companies such as local pharmaceutical or medical device companies, and individual doctors or researchers aligned with research organisations. Trials may be conducted at a single site in a health facility or research institute, across multiple sites in one or several jurisdictions across Australia, or across multiple centres internationally.

In Australia, the trial sponsor is responsible for the investigational product or device, the clinical trial protocol and for notifying the Therapeutic Goods Administration (TGA) of any serious and unexpected adverse medical events that occur during a clinical trial. Clinical investigators are required to obtain ethics approval for their research, notify the approving ethics committee and sponsor of any adverse medical events, and coordinate the conduct of the research across multiple sites. In Australia, hospitals and other state and territory government health-sector trial sites, including private institutions, are ultimately responsible for deciding whether a clinical trial proceeds on their premises.

### The clinical trials landscape

The Australian clinical trials and health and medical research environment has been described as complex. This is attributed to the large number of diverse stakeholders operating in the sector with varying and often overlapping levels of responsibility, purpose and activities. [33,37] The stakeholders involved in the clinical trials sector include Australian Government agencies, state and territory governments, public and private hospitals, universities and research institutions, private organisations, companies' inter-jurisdictional committees and working groups, and trial participants and patient advocacy groups (Box 2).

#### Box 2

#### Stakeholders in Australian clinical trials

Australian Government departments, affiliated agencies and initiatives

- Council of Australian Government Health Council
- Australian Government Department of Health
- Australian Commission on Safety and Quality in Healthcare
- Australia Institute of Health and Welfare (AIHW)
- Department of Industry, Innovation and Science
- Medical Research Future Fund (MRFF)
- National Health and Medical Research Council (NHMRC)
- Therapeutic Goods Administration (TGA)

#### State and territory governments

- Departments of Health
- Local health districts/boards
- Public hospitals and health facilities
- Clinical trials networks
- Medical research institutes
- Human research ethics committees (HREC) and research governance offices (RGO)

Private hospitals, health facilities and organisations/companies

Industry and peak/key industry groups and organisations

- International and local pharmaceutical, biotechnology and medical technology companies
- Medicines Australia
- MTP Connect
- Australian Clinical Trials Alliance (ACTA)

Inter-jurisdictional working groups and associated forums

- Clinical Trials Collaborative Forum and participating organisations
- Clinical Trials Project Reference Group (CTPRG)

University and other teaching and research institutions

**Trial participants** 

Patient and consumer groups

Researchers, investigators, clinical trials/research staff and health professionals

Similar to Canada, Australia does not have a single, overarching government body or entity with national authority to effect positive change, or provide oversight for governance formation, regulation enactment and policy development. [33,37]. No single level of government or industry controls all the levers to effect change in the clinical trials sector. In this context, the Australian Government Department of Health in collaboration with the CTPRG is continuing to lead clinical trial sector improvements consistent with the Council of Australian Governments Health Council reform agenda. Until the introduction of the Medical Research Future Fund, the NHMRC historically was the national organisation with the function of health and medical research funding and the development of advice. It has either undertaken or overseen several previous clinical trial reform initiatives, such as the *Good Practice Process for Site Assessment and Authorisation Phases of Clinical Trial Research Governance* [138] and the Human Research Ethics Application (HREA) as a replacement for the National Ethics Application Form (NEAF).<sup>67</sup> However, the NHMRC's legislatively defined responsibilities, governance structure, and designated authority as an independent statutory agency, prevent it from assuming the role of an independent champion and overarching leader to drive and coordinate reform in the health and medical research sector.[37]

Multiple entities currently shape the sector's policy environment and are involved in the organisation and operational governance of clinical trials in Australia. This includes market participants (sponsors, researchers, clinical investigators and trial participants), the biotechnology, pharmaceutical and medical technology industries, not-for-profit associations, health organisations, academic institutions, government agencies and affiliated bodies at national, state and territory level.

The regulation of clinical trials operates at a number of levels under both Commonwealth and state and territory legislation. In addition, there are various responsibilities resting with trial sponsors, human research ethics committees (HRECs), the approving authority (institution) and investigators.<sup>68</sup> Below is an overview of clinical trials governance and regulation in Australia.

### Australian Government

Clinical trials and health and medical research crosses several Australian Government portfolios. The government departments and affiliated agencies are listed in Box 2.

### **Therapeutic Goods Administration**

Therapeutic goods<sup>69</sup> are regulated in Australia under the *Therapeutics Goods Act 1989*, the *Therapeutic Goods Regulation 1990*, and the *Therapeutics Goods (Medical Devices) Regulations* 2002. The TGA is responsible for administering the Australian therapeutic goods legislation.

The TGA is a division of the Australian Government Department of Health and is Australia's regulatory authority to monitor the safety of medicines and other therapeutics such as medical devices and biologicals. The TGA oversees the inclusion of medicines and medical devices for human use on the Australian Register of Therapeutic Goods (ARTG). This includes therapeutics that are either imported or manufactured in Australia, or exported. Unapproved medicines or medical devices to be provided to trial participants in a clinical trial require notification under the Clinical Trial Notification (CTN) Scheme or exemption through the Clinical Trial Exemption (CTX) Scheme. Under the CTN scheme, scientific and ethical review is provided by a HREC with subsequent notification to the TGA. Under the CTX scheme, the TGA has a direct role in the review of trial scientific data and must give approval for the proposed trial program to go ahead and HREC review is also required.

### National Health and Medical Research Council

The NHMRC is Australia's key expert body promoting the development and maintenance of public and individual health standards.<sup>70</sup> The NHMRC also has a major role in the funding of health and medical research. The NHMRC has been charged with implementing previous Australian Government measures Expediting Clinical Trials Reforms and Simplified and Consistent Health and Medical Research, through initiatives such as 1) increasing the capability of the academic clinical trial workforce through the development of education and training programs, 2) establishing a fully functional clinical trials web portal, and 3) a nationally consistent approach to the site approval of clinical trials in order to reduce complexity and accelerate the clinical trials review process in both the public and private health sectors.

### **Medical Research Future Fund**

The Australian Government announced the establishment of the \$20 billion Medical Research Future Fund (MRFF) in the 2014–15 Federal Budget, to provide a sustainable source of funding for vital medical research over the medium to longer term.<sup>71</sup> The MRFF will from 2020-21 effectively double Australia's investment in health and medical research. MRFF funding is additional, and complementary to, the work of the NHMRC.

The *Medical Research Future Fund Act 2015* sets out the rules for the development of the Australian Medical Research and Innovation Strategy and Australian Medical Research and Innovation Priorities by the Australian Medical Research Advisory Board. The MRFF provides grants of financial assistance to support health and medical research and innovation to improve the health and wellbeing of Australians. It operates as an endowment fund with the capital preserved in perpetuity. To date, \$1.7 billion in MRFF investments have been announced including over \$260 million to support clinical trials.

# Key industry and sector organisations

### **Medicines Australia**

Medicines Australia (MA) represents the discovery-driven pharmaceutical industry in Australia through its advocacy, educational and inter-jurisdictional relationship-building activities. Membership of MA includes local and international organisations involved in the innovative medicines industry.

### **MTP** Connect

MTP Connect is a not-for-profit organisation that aims to accelerate the rate of growth of the medical technologies, biotechnologies and pharmaceuticals sector to achieve greater commercialisation and establish Australia as an Asia-Pacific hub for MTP companies. It was formed in November 2015 as part of the Australian Government's \$250 million Industry Growth Centres Initiative.

### Australian Clinical Trials Alliance (ACTA)

ACTA was established in 2013 with seed funding initially provided by the Victorian Government as a national peak body comprising clinical trial networks, clinical trial coordinating centres and clinical quality registries across Australia. Its platform is to support and represent the networks of clinician researchers that conduct investigator-initiated or clinical trials within the Australian health system. The mission of ACTA is to promote effective and cost-effective healthcare in Australia through investigatorinitiated clinical trials and clinical quality registries that generate evidence to support decisions made by health practitioners, policymakers, and consumers. It has since received funding support from a range of other sources, including Commonwealth and jurisdictional governments.

Most recently, ACTA received funding of \$5 million under the MRFF in 2016-17 over five years to enhance the capacity of clinical trial networks (CTNs) across a number of specialities, allowing investigators and service providers to identify and evaluate new approaches to optimise healthcare effectiveness. In this way, ACTA fulfils the role of a national alliance partner to provide highly specialised leadership and support to build critical capability in the health and medical research sector essential to driving this component of Australia's innovation economy. It brings together CTNs, large trial coordination centres, and relevant Clinical Quality Registries (CQRs) to enhance the work and outcomes of investigator and sponsor-led clinical research. It provides best practice models of operation by working with sites and trial coordinators, supports professional development, knowledge exchange and multi-disciplinary collaboration, and actively engages in translation and commercialisation.

### State and territory governments

Each jurisdiction, through their respective departments of health and affiliated agencies, is responsible for overall management of the health districts and/or public health organisations within its state or territory. This includes public hospitals where a large proportion of clinical trials in Australia are conducted.

# Inter-jurisdictional networks and working groups

There is currently no single entity that has responsibility for change in the clinical trials sector. Therefore, several bodies were established to support a collaborative and partnership approach to improving the clinical trials environment in Australia:

- Clinical Trials Project Reference Group (CTPRG)
- Clinical Trials Collaborative Forum
- The former National Mutual Acceptance Jurisdictional Working Group (NMAJWG)
- The former Clinical Trials Advisory Committee (CTAC).

### **Clinical Trials Project Reference Group**

In recognition of the important role that state and territory jurisdictions and hospitals have in progressing change in the clinical trials sector in Australia, the Clinical Trials Jurisdictional Working Group (now known as the Clinical Trials Project Reference Group) was formed in 2014 and reports through the Council of Australian Governments Health Council structure.

The purpose of the CTPRG is to identify and implement actions and system redesign that will enable a streamlined and consistent national approach to clinical trials within Australia with the intention of enhancing health outcomes and building Australia's ability to attract national and international clinical trials. The CTPRG members are senior officials from all jurisdictional health departments, and the TGA and the NHMRC. The CTPRG works in collaboration with a range of key stakeholders including industry, senior officials from state and territory health departments and the NHMRC, to progress its program of work.

### **Clinical Trials Collaborative Forum**

In recognition of the complex landscape and dispersed responsibilities associated with the conduct of clinical trials in Australia, the Clinical Trials Collaborative Forum (the Forum) was established in 2017 as a shared desire by government, non-government and industry to make Australia a preferred destination for clinical trials. The primary purpose of the Forum is to identify issues, exchange information and engage in collaborative problem solving. Participation in the Forum includes representatives from industry (including Medicines Australia, AusBioTech, and the Australian Clinical Trials Alliance), NHMRC, TGA and members of the CTPRG.

### **Clinical Trials Advisory Committee**

The former Clinical Trials Advisory Committee (CTAC) was established in 2014 to provide advice to the Department of Health and the Department of Industry and Science on various measures under the clinical trials reform initiative. Membership was drawn from senior representatives of the Australian Government and state and territory governments, industry, academic trials and consumer groups.<sup>72</sup> CTAC has now been disbanded.

### National Mutual Acceptance Jurisdictional Working Group

The former National Mutual Acceptance Jurisdictional Working Group (NMAJWG) was formed cooperatively by jurisdictions in 2013 and previously reported through AHMAC. It was created to oversee implementation of the National Mutual Acceptance Scheme for single ethics approvals.<sup>73</sup>

# Clinical trials regulatory framework in Australia

In Australia, as in other developed and developing countries, there is a strong regulatory framework for the conduct of clinical trials to ensure the safety of people who participate in clinical trials. This includes regulatory oversight and the requirement for ethical review as described below.[139]

### **Clinical Trial Notification Scheme**

The TGA provides a legislated regulatory framework for the availability of medicines, medical devices and biologicals within Australia. There are two TGA schemes under which clinical trials involving unapproved therapeutic goods may be conducted, the CTN Scheme and the CTX Scheme. The CTN scheme enables drugs and devices not registered on the Australian Register of Therapeutic Goods (ARTG) to be used in clinical trials, following notification to the TGA (use of notified products in a trial can only proceed following Human Research Ethics Committee [HREC] and site-specific approvals for the trial). The TGA has made a number of recent improvements to CTN to support broader reforms, including the transition to an on-line submission and approval system (eCTN). The CTX scheme is a TGA approval process under which it assesses the evidence and approves the safety of proposed usage guidelines within individual trial protocols, prior to HREC and site-specific approvals.

The TGA's CTN/CTX scheme is often recognised as one of the fastest and most efficient regulatory processes for clinical trials globally.

### Ethical review of clinical trials

By design, clinical trials are concerned with maintaining internal validity, that is, the delivery of the investigational product in well-defined populations of interest to demonstrate the safety and efficacy of medicines, devices and therapeutic interventions, and the safe delivery of these to the broader population. Society expects the safety of research participants, integrity of research conduct and effective use of public funds to support research. To this end assurity is provided through the rigorous scientific and ethical review of clinical trials.

The framework, systems and processes leading to the authorisation and commencement of a clinical trial at a trial site is known as 'research governance.'[138] Proposals for the ethical approval of clinical trials are assessed by a human research ethics committee (HREC). The function of the HRECs is guided by relevant standards including those outlined in the *National Statement on Ethical Conduct in Human Research (2007, updated May 2015)* issued by the NHMRC. The national statement sets out the requirements for the formation and operation of HRECs and the relevant ethical principles and values by which research should be designed and conducted, and to which HRECs should refer when reviewing research proposals. HRECs are essential for the ethical oversight of research involving humans. HRECs review research proposals involving human participants to ensure they are ethically acceptable and in accordance with relevant standards and guidelines.[140] There are more than 200 HRECs in institutions and organisations across Australia.

## National Approach to Single Ethical Review

Under the National Approach to Single Ethical Review, the NHMRC has certified the ethical review processes of 45 institutions, representing 49 HRECs. Many of these, because of their expertise, have been certified to assess applications for clinical trials that require ethical review by a HREC and governance or site-specific approval. Hospitals rely on advice from bodies such as HRECs on whether the proposed clinical trial complies with the principles of ethical behaviour set out in the national statement.

The objective of the National Approach to Single Ethical Review of Multi-centre Research, formally known as the Harmonisation of Multi-Centre Ethical Review, is to enable the recognition of a single ethics and scientific review of multi-centre human research within, or across, Australian jurisdictions.<sup>74</sup> The benefits of adopting a national approach to single ethics review of multi-centre research include:

- The time taken from ethics review application to research start-up is shorter
- Australia's attractiveness as a place for international investment in commercially sponsored clinical trials is enhanced
- Public confidence in the rigour of Australia's system of ethics review of human research is maintained due to the standardisation of ethics review processes
- The roles and responsibilities of the researcher, the institution, the HREC and other key stakeholders in the conduct of multi-centre research are clear and consistent.

A central component of the national approach is the National Certification Scheme of Institutional Processes Related to the Ethical Review of Multi-centre Research, which provides a level of assurance that an institution's ethics review processes conform to nationally consistent standards.

### **National Certification Scheme**

The National Certification Scheme provides assurance that the policies, processes and procedures of an institution and its HREC comply with an agreed set of national criteria for the conduct of an ethics review of multi-centre human research. Institutions and their HRECs that have had their ethics review processes certified through the National Certification Scheme, and which undertake ethics review of multi-centre research proposals, can have that review accepted by any institution within any jurisdiction, without the need for a separate, additional, ethics review.

Participation in the National Certification Scheme is voluntary. In order for an institution to be certified, its ethics review processes undergo an independent assessment conducted by the NHMRC. Certification begins with the institution carrying out a self-assessment of its ethics review processes and supporting structures against agreed national criteria. This is followed by a desktop assessment by NHMRC and a panel of independent assessors before an on-site visit to verify institutional claims and practices.

Certification depends upon satisfactory demonstration of institutional conformance to specified criteria which, in part, is based on the national statement or any document that complements, supplements or succeeds it. Certification also respects institutional decisions regarding whether research should be conducted at a given site. Advice received from a HREC undertaking the single ethics review does not replace the need for local institutional decision-making on matters of research governance.

### **National Ethics Application Form**

As part of the initiative to streamline ethics approval, the NHMRC has developed the Human Research Ethics Application Form (HREA) as a replacement for the National Ethical Application Form (NEAF). The stated aim of the HREA is to be a concise application to facilitate efficient and effective ethics review for research involving humans, and to assist researchers to consider the ethical principles of the *National Statement on Ethical Conduct in Human Research (2007)* in relation to their research, rather than focus on requirements for approval.

### National Mutual Acceptance Scheme

In 2013, the Victorian, South Australian and Queensland departments of health, and the New South Wales Ministry of Health, signed a memorandum of understanding for the National Mutual Acceptance (NMA) of ethics and scientific review of clinical trials conducted in each of the participating jurisdictions' public health organisations. The NMA allows public health organisations of participating jurisdictions to accept a single ethical and scientific review of multi-centre clinical trials conducted by an appropriate NHMRC-certified HREC. In December 2015, the scope of the NMA was expanded beyond clinical trials to include all human research. In 2016, the Australian Capital Territory joined the NMA and Western Australia joined in 2017. In order for ethics reviews of human research to be accepted under NMA, the HREC conducting the review must be under the authority of an institution certified under the NHMRC National Certification Scheme, and also be a certified reviewing HREC under the NMA scheme.<sup>75</sup> The NMA scheme has consistently been identified as a key enabler for clinical trials in Australia. For trials approved under the NMA scheme, ethics approval could be considered on par with international competitors.

### Local-site research governance

Local-site research governance refers to the processes used by institutions to ensure that they are accountable for the research conducted under their auspices. To be properly governed, research must be conducted according to established ethical principles, guidelines or policies. Elements of research governance include ethical approvals, compliance with legislation, legal assurances (provided contractually and with adequate insurance and indemnity). More specifically, site-specific assessment, is concerned with institutional policy and procedures for responsible research conduct, and managing research misconduct, reporting requirements, credentialing and training of researchers, and managing institutional risk.

Individual public health institutions and research organisations are responsible for research governance, which involves ensuring that the institution has the capacity to undertake the trial and, that necessary contractual and insurance arrangements are in place. Public health officers (PHO), often referred to as research governance officers, are required to undertake a sitespecific assessment for each research project, thereby allowing the organisation to consider whether it has the capacity to conduct the trial at the site. The site-specific assessment (SSA) considers physical resources, staff, insurance and indemnity requirements, and other matters. The site-specific assessment is undertaken by a research governance officer (RGO). It is possible for the site-specific assessment and HREC ethical and scientific review to occur in parallel; however, the decision to authorise or deny the commencement of a research project is only made by the PHO when the responsible HREC has granted the approval and the SSA has been satisfactorily completed.

### **Clinical trials registration**

It is a requirement within the principles of good clinical practice (GCP) for the conduct of research that a clinical trial is registered and publicly accessible. Clinical trial registration is the process whereby key details about the design, the medicine or the therapeutic intervention to be tested are made available to an accessible database or registry. In Australia, registration is not currently mandated in the National Statement but is anticipated to occur before the first participant is enrolled in a trial. In Australia, the Australian and New Zealand Clinical Trials Registry (ANZCTR) is one of the primary registries in the World Health Organization (WHO) registry network. The other registry is **Clinicaltrials**. gov which is a USA registry that lists clinical trials in the USA as well as other countries, including Australia.<sup>76</sup> The ANZCTR is a key part of Australia's clinical trials infrastructure (http:// www.anzctr.org.au/). On behalf of the CTPRG, the Commonwealth Department commissioned a review of the current registry compared to international best practice to identify options for a potential next generation registry in Australia. The outcomes of the Review are expected to be available in late 2018.

## Research principles and guidelines for Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. The standard also protects the rights, integrity and confidentiality of trial subjects. There are several documents and guidelines that detail the principles of good clinical practice in Australia including:

- Note for guidance on clinical safety data management – definitions and standards for expedited reporting which describes the reporting processes for expedited reporting of adverse drug reactions in clinical trials [141]
- ISO 14155 Clinical investigation of medical devices for human subjects Good Clinical Practice – this document articulates

standards for the design, conduct, recording and reporting of safety or performance of medical devices for regulatory purposes<sup>77</sup>

- Australian Clinical Trial Handbook [142]
- Australian Code for the Responsible Conduct of Research [143]
- World Medical Association Declaration of Helsinki<sup>78</sup>
- Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Figure 8: Overview of the Australian approach to clinical research governance



### Initiatives and reviews undertaken in the clinical trials sector

In response to the perceived decline in clinical trial activity in Australia, several high-level government and industry-led reviews of the clinical trial landscape have been conducted which focus on the need to improve the competitiveness and timeliness of clinical trials in Australia in order to attract more global investment including:

In recognition of the important role that state and territory jurisdictions and hospitals have in progressing change in the clinical trials sector in Australia, the Clinical Trials Jurisdictional Working Group (now known as the Clinical Trials Project Reference Group) was formed in 2014 and reports through the Council of Australian Governments Health Council structure.

The purpose of the CTPRG is to identify and implement actions and system redesign that will enable a streamlined and consistent national approach to clinical trials within Australia with the intention of enhancing health outcomes and building Australia's ability to attract national and international clinical trials. The CTPRG members are senior officials from all jurisdictional health departments, and the TGA and the NHMRC.

The current CTPRG Implementation Plan has the following objectives:

- Streamline coordination units and innovation
- Harness national networks and partnerships
- Improve clinical trials data and knowledge systems
- Embed research as essential health system business
- Enhance capacity and consistency of ethics approvals.

### Framework for National Aggregate Statistics

A significant deliverable to date has been agreement on a Framework for National Aggregate Statistics (NAS) for metrics to provide governments with reliable national information on clinical trial activity, and to support and measure the effectiveness of activities designed to improve the environment for trials in Australia. This Framework was approved by the Australian Health Ministers Advisory Council (AHMAC) and Council of Australian Governments Health Council in 2015 and includes the following foundational metrics:

- 1. Number of new trials and breakdown by trial phase, and by sponsor type
- 2. Overall study start-up timeline (regulatory timeline)
- 3. Ethics and governance approval timeline
- 4. Human Research Ethics Committee (HREC) approval timeline
- 5. SSA/site assessment timeline
- 6. Rrial recruitment: actual and planned number of participants recruited
- 7. Site recruitment: actual and planned number of participants recruited
- 8. Total inbound (internal and external) investment annually.

The second (interim) report under the Framework for NAS was published in 2017. It included data for clinical trials from all sponsor types in five jurisdictions and provided the most reliable and comprehensive national picture to date for clinical trials in public health organisations in Australia.

When fully implemented across all jurisdictions, national data will be available for the first time across a set of key strategic and operational objectives to drive quality improvement within the sector and to position Australia as a preferred location for clinical trials.

### Scoping and Analysis of Recruitment and Retention in Australian Clinical Trials

Participant recruitment has been identified as a key issue for the clinical trials sector in Australia and was an identified priority for CTPRG.

In 2015 the Australian Government Department of Health contracted Ernst and Young (EY) on behalf of the CTPRG to undertake scoping and analysis of issues in recruitment and retention in Australian clinical trials. EY was asked where efforts could be more effectively directed to enhance clinical trial recruitment in Australia, and undertook broad consultations as part of its research.

The final EY Report includes a range of recommendations to address barriers to, and enhance enablers for, clinical trial recruitment and retention in Australia. Highlights include recommendations calling for: collaborative government leadership; establishment of dedicated structures at national and individual state and territory levels to improve clinical trial coordination and administration across Australia; sustainable recruitment strategies for research nurses to enhance clinical trials workforce capacity; and coordinated use of clinical trial networks and Clinical Quality Registries (CQR) to improve recruitment and retention, better reflect national, consumer and community priorities for research, and stimulate clinical trial activity.

### Analysis of Recently Conducted Clinical Trials

In 2015 the Australian Government Department of Health contracted an analysis of the critical success factors and reasons for failure of recent clinical trials in Australia. The focus was on pharmaceutical and medical device clinical trials conducted within last five years that were commercially funded, and conducted in more than one jurisdiction. Key enablers of successful clinical trial conduct in Australia identified by the research included:

- Clinical Trials Notification (CTN) scheme enabling quick regulatory timeframes
- National Mutual Acceptance Scheme and reduced duplication in ethics approval documentation
- Short ethics review timeframes for private sites
- Experienced researchers and site study coordinators who can positively impact timely ethics and governance approvals, patient recruitment and provision of quality data
- Standardised costing or corporate 'fair market stipulations' to assist with budget negotiations
- Robust feasibility assessments and honest patient recruitment estimates
- Established referral networks and national patient databases.

Key barriers or reasons for failure of clinical trial conduct identified in the report included:

- No national single ethics approval process, impacting time to trial start up and/or requirement for multiple ethics submissions and approvals
- Reluctance of sites to become lead sites for ethics submissions due to additional work involved
- Risk for companies associated with single ethics submission, as delays at that site can impact time to trial start up

- Lack of consistency in Human Research Ethics Committee (HREC) requirements
- Lack of clarity, consistency, transparency and timeliness of governance approvals
- Inability for sponsor organisation to communicate directly with HREC or Research Governance Officer at sites
- Inaccurate feasibility assessments and unclear accountability for delivering recruitment targets within institutions
- Lack of awareness and support for clinical research in Australia.

### Australian New Zealand Clinical Trials Registry (ANZCTR)

The ANZCTR is an online public registry of clinical trials and has been identified as a key part of Australia's clinical trials infrastructure. On behalf of the CTPRG, the Australian Government Department of Health contracted a review of the current registry compared to international best practice, and identify options for a potential next generation registry in Australia. The outcomes of the Review are expected to be available in late 2018.

### **Clinical Trial Governance Framework**

Development of a Clinical Trials Governance Framework is a key deliverable for the CTPRG and on behalf of the CTPRG, the Australian Government Department of Health procured the Australian Commission on Safety and Quality in Health Care to develop the Framework in September 2017. The Framework is scheduled for delivery in June 2019.

### Council of Australian Governments Health Council – revitalised clinical trials agenda

Australia has the objective of being a preferred destination for clinical trials. Achieving this goal requires cooperation between governments (Commonwealth, states and territories) as no one entity controls all the levers that support trial activity (i.e., funding, ethics and governance).

Following a Council of Australian Governments Health Council directive in April 2016, all jurisdictions collaborated (via CTPRG) to develop a set of principles and priority action areas to enhance the capacity of the clinical trial sector to improve administrative efficiencies, better engage sponsors and improve trial start up times and outcomes. Council of Australian Governments Health Council agreed in March 2017 to further strengthen Australia's clinical trial sector through a new revitalised agenda for reform, using stimulus from the Commonwealth's \$7 million *Encouraging more clinical trials in Australia* initiative to support jurisdictional redesign of clinical trial operations around coordination hubs. Priority action areas identified in the Council of Australian Governments Health Council revitalised clinical trials agenda include:

- Coordination units new models to centralise and coordinate trial management
- Networks and partnerships maximised collaboration with trial networks, communities of expertise/practice and registries, with an emphasis on crossjurisdictional and discipline cooperation
- Enhancement of data and knowledge systems – fast-tracked agreed metrics collection and improved data linkage capability, and support for mutual acceptance of ethical review
- Research as essential health system business – embedding research and clinical trials into core hospital governance arrangements, including the use of performance measures
- Embedding clinical trials in safety and quality approaches – including collaboration with the Australian Commission for Safety and Quality in Health Care to establish a governance framework to support research in public hospitals.

The Commonwealth in collaboration with the CTPRG is continuing to lead clinical trial sector improvements consistent with the Council of Australian Governments Health Council reform agenda.

### **Clinical Trials Collaborative Forum**

In recognition of the complex landscape and dispersed responsibilities associated with the conduct of clinical trials in Australia, the Clinical Trials Collaborative Forum was established in 2017 as a shared desire by the government, non-government and industry to make Australia a preferred destination for clinical trials. The primary purpose of the Forum is to identify issues, exchange information and engage in collaborative problem solving.

### National Mutual Acceptance Scheme

The former National Mutual Acceptance Jurisdictional Working Group (NMAJWG) was formed cooperatively by jurisdictions in 2013 and previously reported through the Australian Health Ministers' Advisory Council (AHMAC). It was created to oversee implementation of the National Mutual Acceptance scheme for single ethics approvals and advise on all relevant matters.

The NMA scheme has consistently been identified as a key enabler for clinical trials in Australia. For trials approved under the NMA scheme, ethics approval is now largely on par with international competitors.

### **Therapeutic Goods Administration**

The TGA provides a legislated regulatory framework for the availability of medicines, medical devices and biologicals within Australia. There are two TGA schemes under which clinical trials involving unapproved therapeutic goods may be conducted, the CTN Scheme and the CTX Scheme. The CTN scheme enables drugs and devices not registered on the Australian Register of Therapeutic Goods (ARTG) to be used in clinical trials, following notification to the TGA (use of notified products in a trial can only proceed following Human Research Ethics Committee [HREC] and site-specific approvals for the trial). The TGA has made a number of recent improvements to CTN to support broader reforms, including the transition to an on-line submission and approval system (eCTN). The CTX scheme is a TGA approval process under which it assesses the evidence and approves the safety of proposed usage guidelines within individual trial protocols, prior to HREC and site-specific approvals.

The TGA's CTN/CTX scheme is often recognised as one of the fastest and most efficient regulatory processes for clinical trials globally.

#### Standard pricing for clinical trials

In addition to these initiatives, the Independent Hospital Pricing Authority (IHPA) engaged with stakeholders in 2013 to develop a standard table of pricing for clinical trial items.

### Australian state and territory initiatives

Most state and territory departments of health have a designated branch or office responsible for research as listed below. Their responsibilities encompass policy development, managing research grants and fellowships, establishing and overseeing research ethics and governance policies, and providing a central point of contact for researchers, research managers and study sponsors.

- New South Wales (NSW) Ministry of Health – Office for Health and Medical Research (OHMR)
- Queensland Health Department– Health Innovation, Investment and Research Office (HIRO) which sits within the Office of the Director-General
- Victorian Department of Health and Human Services – Centre for Evaluation and Research and Health
- South Australia (SA) Health Office for Research
- Western Australia (WA) Department of Health – The Research Development Unit
- Australian Capital Territory (ACT) Health– Office of Research
- Northern Territory no specific department
- Tasmanian Department of Health Research Governance Unit.

A snapshot of reform activities being undertaken in several Australian jurisdictions is provided below. The NSW Ministry of Health has a number of initiatives under way to foster and nurture a research culture in their organisation and to embed research into everyday health practice. [144,145]

### **NSW Ministry of Health**

The NSW public health system is the largest public health system in Australia, comprising 17 local health districts and specialty health networks, 228 hospitals and 114,000 FTE staff. In 2011, the NSW Government established the Health and Medical Research Strategic Review to develop a 10-year plan. The plan identified NSW's strengths and advantages to support health and medical research and made recommendations on improving the way research resources are developed and managed, including encouraging research and innovation in health services, leadership in clinical trials, strengthening the research workforce, and improving NSW Health research administration and infrastructure. The OHMR was established to implement this 10-year strategy.

### Key outcomes

**NSW research hubs** – Sydney Health Partners and the Sydney Partnership for Health, Education, Research and Enterprise (SPHERE) recognised by the National Health and Medical Research Council as an Advanced Health Research Translational Centre, and Regional Health Partners recognised as a Centre for Innovation in Regional Health.

#### NSW Research Ethics and Governance Reform Framework and Action Plan – Developed in

2014 as part of the NSW Health and Medical Research Governance Reform Project to improve the health and medical research pre-approval process and reduce barriers to undertaking clinical trials in NSW. The Framework and Action Plan has been endorsed by the chief executives of all local health districts (LHD) and related agencies.

### Collection of ethics and governance metrics -

From 1 July 2016, the OHMR began collecting data from NSW LHDs, specialty health networks (SHN) and NSW Ambulance to generate ethics and governance metrics for health and medical research, including clinical trials. The collection of data for, and analysis of, four of the metrics has been incorporated into the 2017 –18 chief executive service agreements.

**Research Ethics and Governance Information System (REGIS)** – A joint initiative between eHealth and the OHMR. REGIS is intended to support the ethics and governance management of human research projects in all NSW and ACT public health organisations. REGIS will replace AU-RED and the online forms portal as one system, accessible by researchers and public health organisations administering research.

**Early Phase Clinical Trials Framework for NSW** – Developed by the OHMR, the framework is designed to strengthen the capability in NSW to engage in national and international early phase trials.

**Medical Research Support Program** – Provides infrastructure funding to support the day-to-day costs of running independent medical research institutes in NSW. The 2016 –20 round of funding has \$48.6 million allocated for 15 institutes in 2016 –17. An additional \$1.2m was provided to two institutes to assist with a merger or restructuring.<sup>79</sup>

### Western Health, Victoria

Western Health in Victoria services approximately 800,000 residents of the western region of Melbourne. It manages three acute public hospitals (Footscray, Sunshine and Williamstown), a day hospital at Sunbury, a transition care facility at Williamstown and a large drug and alcohol service at Footscray. Western Health espouses a strong philosophy of working with its local community to deliver excellence in patient care.

### Integrating and embedding research in health service delivery

Western Health has recognised the importance of strengthening and fostering research to provide the evidence base for practice and is committed to driving research and quality improvement activities as part of everyday practice. Western Health's focus is on becoming a leader in translational and health services research that addresses the healthcare needs and expectations of their local community. In 2015, Western Health established and embedded the Research Roadmap 2015 - 2020 which is aligned with the Western Health Organisational Strategic Plan 2015 –2020. The research roadmap articulates the strategic direction for research at Western Health. It also identifies several challenges facing research at Western Health. These include limited dedicated research time for clinicians; balancing priorities between service delivery and research activities, particularly in relation to accessing clinical support services for research studies such as diagnostic services; and lack of formal organisational accountability for research across Western Health. Several key strategic opportunities were identified in the research roadmap to build Western Health's research profile including continuing to create an environment that prioritises research at all levels across the organisation, and building governance arrangements to support this, as well as promoting and supporting research capacity and capability.

### Development of whole-of-organisation outcome measures to monitor research success

To improve the sustainability of research at Western Health six key actions have been articulated:

Action 1: Increase awareness of the importance of research to underpin best care

Action 2: Support high-quality research that reflects Western Health's organisational strategy

Action 3: Build research capacity across Western Health

Action 4: Expand research capacity and foster innovation

Action 5: Enhance community and consumer engagement

Action 6: Strengthen and sustain research partnerships

A series of activities and associated metrics have also been developed for each action to measure and monitor whole-of-organisation commitment to delivering research outcomes and timelines for delivery.

For example, with regard to Action 2, the focus is on establishing strong governance arrangements to support research growth and emphasising accountability across the organisation for undertaking research. Key activities to support Action 2 include establishing and embedding key performance indicators at a unit and divisional level, and developing and embedding annual business planning research actions for each division and directorate aligned to best care and research focus areas.<sup>80</sup>

### Western Australia

Western Australia Health has implemented the Western Australia Health Research Governance Framework. The framework governs the scientific, ethical and governance review and approvals of clinical trials, and oversees the conduct and monitoring of human research within the WA public health organisation. The framework aims to ensure effective and consistent research activity across the WA health system through:

- Single ethical review of multi-centre research
- Introduction of research governance and single ethical review standard operating procedures
- Standard ethics and governance forms and agreements
- Implementation of the Research Governance Service which is a centralised information technology system for investigators, project members, sponsors, site administrators, human research ethics committees and research governance offices. The Research Governance Service enables the completion, submission, administration, tracking and reporting of ethics and governance applications through the ethics approval and site authorisation processes.

### Conclusion

The Australian clinical trial stakeholder landscape is complex, and no single government or agency holds all the levers for change. A number of reviews have been conducted in Australia to identify barriers in the clinical trial operational environment and a number of initiatives have been undertaken to incentivise the sector. These have largely focused on per-patient costs, medical expertise, data quality, the reliability of sites to recruit patients and the timeliness of site start-up and local-site governance approval. Additionally, the Commonwealth has undertaken a number of initiatives including:

- Promoting consistency in safety monitoring and reporting of clinical trials for improved transparency
- Tracking site-trial processes timelines
- Training for trial staff through developing learning modules for clinical trial site staff
- Supporting development of a vocational education and training accredited training course
- Providing a reporting portal for trial sites
- Providing support for networks and developing a website for trial sponsors and to raise public awareness of clinical trials more broadly (www.australianclinicaltrials.gov.au).

Besides market participants, it consists of a multiple set of bodies that shape the sector's policy environment. This includes government agencies and government-affiliated bodies at state, territory and federal level, not-for-profit associations and health organisations. All stakeholders have different responsibilities, scope and roles, and can be considered on a spectrum from advisory to decision making bodies.

In addition to the policy landscape, multiple stakeholders are involved in the organisation and operational governance of clinical trials in Australia. However, not all actions needed to drive improvements rest with governments. While sponsors, clinical investigators and participants ultimately drive the conduct of clinical trials; health system managers, the biotechnology, pharmaceutical and medical technology industries are pivotal to advancing the sector. Achieving success requires a collaborative approach between all players beginning with improved governance and a national approach to the accreditation of those Australian health services undertaking clinical trials.

# Appendix 1

- Table 7:
   Canadian Clinical Trial Summit recommendations, strategies and anticipated outcomes
- Table 8:
   Main themes identified in the Rawlins Review and recommendations and actions
- Table 9: UK reports and policy documents
- Table 10: Australian reports and reviews into clinical trials and medical health research

Recommendation	Strategy	Outcomes to date (2017)
1. Establish an implementation and coordination headquarters and resources	Establish or leverage a clear, respected and trusted body to oversee the improvement activities in Canada, to ensure that activities within the action plan can be coordinated, prioritised, structured for maximum fit, measured and monitored. In addition, it would also serve as a national coordinating body for linking and leveraging across research domains and inter-provincial CT improvement activities and initiatives where needed; act as a contact body for issues that need to be noted; and signal internationally Canada's intention to improve the CT landscape.	Canadian Clinical Trials Coordinating Centre (CTCC) was launched in 2014. The CTCC is a pan-Canadian clinical trials organisation established for an initial 3-year period to operationalise the 9 recommendations emanating from the 2012 Action Plan. The CTC's mission is to: 'improve the Canadian clinical trial landscape by promoting efficiencies and advocating for the streamlining of CT processes for industry and clinical researchers'. Funding for the CTCC was extended in 2017 to enable it to continue beyond its original mandate. An advisory group comprising experts in the Canadian clinical relation and input on future CTCC projects and initiatives.
<ol> <li>Measure, monitor, manage and market CT performance improvements</li> </ol>	<ul> <li>Draw on available datasets and select, manage and collect meaningful and transparent metrics on clinical trial performance and return on investment that allows Canada to:</li> <li>1) Measure, monitor and discuss progress</li> <li>2) Identify issues</li> <li>3) Demonstrate return on investment for sponsors, sites and all levels of government.</li> </ul>	Initial set of metrics was collected in 2015. A working group was established to collect a more detailed set of metrics including operational metrics. This initiative is to provide a 'pulse check' of Canada's clinical trial performance.
3. Integrate health system and research infrastructure	Integrate health system and research infrastructure to ensure quality and sustainability of infrastructure, staffing, resources and career support for the generation and integration of research.	A joint meeting of provincial clinical trial organisations was convened in 2015 and facilitated by the CTCC to discuss trends and opportunities within the Canadian CT field. Subsequent inter-provincial meetings have been held to foster collaboration and project management, identify emerging issues and challenges in the CT field and prevent duplication of efforts.

Table 7: Canadian Clinical Trial Summit recommendations, strategies and anticipated outcomes

Recommendation	Strategy	Outcomes to date (2017)
<ol> <li>Improve efficiencies of ethics reviews and advance strategic issues such as accreditation</li> </ol>	Leverage appropriate bodies and expertise and undertake a feasibility assessment and proposal for mutual recognition of ethics reviews; provide common templates with minimal variation (a common application form/submission template, common consent form template, common adverse events report forms); predictable internationally competitive turnaround times; sufficiently resourced REBs and CT systems; compliance with the appropriate standards and respect for provincial differences; elements of an accreditation system and information sharing mechanisms for ethics reviews. Also support the work of Health Canada in evaluating standards and accreditation options and explore strategic issues like accreditation and harmonisation.	CTCC collaborating with Health Canada to establish a national strategic leadership forum to champion, shape and direct the development of research ethics on a pan-Canadian level.
5. Develop a database of registries and consider a national patient recruitment strategy	Improve patient recruitment times by developing a database of registries with appropriate consent and privacy considerations that will help to identify patients that may be eligible for clinical trial participation.	In the British Columbia Clinical Research Infrastructure Network Pan-Canadian Survey on Clinical Trial Participation patients were asked about their experiences with clinical trials and what motivated them to join or not join a trial. The Patient Registries project (to be developed) is to complement the Canadian Clinical Trials Asset Map.
<ol> <li>Adopt common standard operating procedures (SOPs), training and certification</li> </ol>	Fund and leverage the Network of Networks (N2) to more broadly disseminate common SOPs and training resources. Work with key stakeholders to develop a site certification approach to identify organisations that have these standards and training in place.	Standard Operating Procedures and Training developed by the (N2).
7. Improve and use the common clinical trials contract	Implement the model Clinical Trials Agreement.	CTCC to develop language for a Canada-wide initiative to standardise clinical trial agreements by providing a standard contract template.

Recommendation	Strategy	Outcomes to date (2017)
8. Optimise intellectual property protection policy and research and development tax credits	Bring IP policy to levels commensurate with Europe within the Canadian-European Union Comprehensive European Trade Agreement. Improve administration of Scientific Research & Experimental Development tax credits so that credits are received in time to offset costs of trials.	Beyond the scope of the CTCC.
9. Signal our interest globally – open a concierge (storefront) service for investors	Provide information on Canada's clinical trials assets, offerings and improvements to international companies. Then develop a storefront service that can provide a centralised access and information point to global companies.	Development of the Canadian Clinical Trials Asset Map. The map was designed to communicate and showcase Canada's clinical research strengths to all stakeholders including CT sponsors and to better enable sponsors to identify clinical research sites and investigators.
10. New recommendation: Relevant emerging requirements	Fair Market Value Project.	To help accelerate clinical trial start-up times CTCC launched the Fair Market Value Project which is aimed at addressing issues in the budget negotiation process. Its focus is on providing tools and resources for a more streamlined and efficient process for finalising clinical trial budgets, especially taking into account provincial and institutional differences.

Theme	Recommendations	Actions
Culture around research	<ol> <li>The UK departments, with the support of other government departments, should communicate the core role of health research to all NHS staff</li> <li>Embed research as a core NHS function.</li> </ol>	<ul> <li>Director-General of NHS research and development to serve as a member of the proposed NHS commissioning board in England</li> <li>Proposed new health research agency (HRA) and key stakeholders to develop key metrics and indicators of research activity and include in the next NHS Operating Framework. The use and publication of the metrics should allow the performance of trusts to be compared and scrutinised by the trust board, research funders and the public</li> <li>An executive director of each trust to be responsible for promoting research within the organisation and reporting research activity (including metrics) at each board meeting.</li> </ul>
NHS research and development	<ol> <li>A new National Research Governance Service should be established as a core component of the new Health Research Agency</li> <li>The National Institute for Health Research should develop a transparent system to formally assess the performance of trusts in approving and undertaking research and use this to inform its funding allocations.</li> </ol>	<ul> <li>NRGS responsibilities:</li> <li>Undertaking all NHS governance checks, ensuring consistent standards and interpretation of requirements for compliance</li> <li>Facilitate new research and development timelines that would require participating trusts to determine local feasibility within 20 working days</li> <li>Recommend projects as suitable for undertaking within the NHS subject to local assessment</li> <li>Maintain up-to-date records on NHS research staff and confirm their competence to conduct research</li> <li>Issue model agreements and provide clarity on costs and payment.</li> </ul>
Clinical trials of investigational medicinal products	<ol> <li>The government, supported by the medicines and healthcare products regulatory agency should seek to influence the European Commission to act quickly to reverse the European Union (EU) Clinical Trials Directive</li> <li>Before revision of the Clinical Trials Directive the medicines and healthcare products regulatory agency should adopt a more proportionate approach to clinical trial regulation</li> <li>The medicines and healthcare products regulatory agency should increase the quality, consistency and timeliness of advice from its clinical trials unit.</li> </ol>	<ul> <li>The directive should be amended to reduce the scope of the directive through the revision of the definitions in Article 2</li> <li>Ensure the approval and monitoring requirements that are proportionate to risk</li> <li>Simplify the requirements for the reporting of adverse events.</li> </ul>

Theme	Recommendations	Actions
Use of patient data in health research	<ol> <li>The Ministry of Justice should undertake a thorough review of the UK Data Protection Act to identify aspects that require clarification in relation to health research so as to inform the planned revisions to the EU directive and subsequent amendments to the UK Data Protection Act</li> <li>The role of Caldicott Guardians should not include the approval of research studies. Instead it should focus on facilitating the delivery of research studies for which approvals relating to data have already been granted by other bodies</li> <li>A system should be developed to allow approved researchers to work with healthcare providers to identify potential patients to be contacted about research studies in which they may want to participate.</li> </ol>	<ul> <li>Clear guidance on interpretation of these Acts to be provided to researchers and healthcare professionals by the Information Commissioner in conjunction with the new HRA</li> <li>The Office of the Information Commissioner and the new HRA to work with the health departments and other stakeholders to provide definitive guidance on this issue. This should state that researchers, or appropriate members of a research team (e.g. research nurses) working on an ethically approved study should be considered part of a clinical care team for the purposes of accessing data to identify eligible patients to be contacted about research studies.</li> <li>The initial contact with those patients should be conducted by a member of the patient's clinical care team and not by a researcher.</li> </ul>
Use of tissue and embryos	<ol> <li>Hair and nails from living subjects are already excluded from the materials covered by the Human Tissue Act. The following exclusions should be introduced: plasma, serum, urine, faeces and saliva.</li> </ol>	
Ethics	12. NRES should lead on improving support and advice for researchers by providing centralised, coordinated guidance and training on ethical issues for health researchers. Institutions engaged in health research should also improve the local availability of ethics advice and the training of local support staff.	<ul> <li>Embed a proportionate approach within the ethics system including implementation of 'proportionate review'.</li> </ul>

Theme	Recommendations	Actions
A new, single health research agency. The key features of the HRA would be:	<ol> <li>A single research regulator – the 'health research agency' (HRA) be established as an arms-length body (from the Department of Health) to align the disparate elements of regulation and oversee the</li> </ol>	<ul> <li>The HRA to include a new national research governance service (NRGS) as a recognisable entity within the HRA and implement timelines for NHS research and development permissions</li> <li>The HRA to conduct an assessment of the Clinical Trials Unit of the</li> </ul>
<ul> <li>Independence</li> </ul>	regulation and governance of health research	Medicines and Healthcare Products Regulatory Agency medicines and
<ul> <li>Strong leadership and expertise</li> </ul>	14. The HKA should work in consultation with the medicines and healthcare products regulatory agency to become	healthcare products regulatory agency and Good Clinical Practice (שריץ) monitoring inspections
<ul><li>Transparency</li><li>Accountability</li></ul>	a one-stop snop for nealth research regulation and support a shift in the medicines and healthcare products regulatory agency 's approach to clinical trial regulation	<ul> <li>The HRA should undertake an evaluation of the differences in law and practice across the UK in the use of human tissue and access to patient data</li> </ul>
<ul> <li>Dialogue with other organisations</li> </ul>	15. The HRA and the regulatory and governance organisations in the devolved nations should work to develop a seamless	<ul> <li>The HRA should be given the necessary authority to oversee the structural and cultural changes to the regulatory and governance environment</li> </ul>
<ul> <li>Flexibility to respond to emerging issues.</li> </ul>	regulatory system for the UK for all aspects of its remit 16. The HRA should support researchers and raise	<ul> <li>Consult with stakeholders to devise published metrics through which its import on scored in the UK and anothermatic montion the follow</li> </ul>
The key functions of the	research standards by providing consistent advice and interpretation of logiclation and a single point	its impact on research in the ON and perior marke in meeting the rout principles can be judged
<ul> <li>Monitor performance</li> </ul>	of contact to ensure better communication in navigating the regulation and governance pathway	<ul> <li>Lead development of a revised research governance framework which establishes a proportionate governance pathway and communicates</li> </ul>
<ul> <li>Proportionate approach</li> </ul>	17. The HRA and the regulation and governance pathway	changes in the responsibilities of different stakeholders
<ul> <li>Guidance, education and training</li> </ul>	which it oversees should operate in accordance with the four principles. And therefore should have the necessary	<ul> <li>Draw on appropriate expertise including from patients and the public.</li> </ul>
<ul> <li>Communications</li> </ul>	authority to oversee the required structural and cultural	
<ul> <li>Public engagement.</li> </ul>	changes to the regulatory and governance environment.	

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Author Title National Institute for Research Governance Policy

Year	Author	Title	Aim(s)
2017	Professor Sir John Bell and Life Sciences Industrial Strategy Board [129]	Life Sciences Industrial Strategy – a Report to the Government from the Life Sciences Sector	The report, commissioned by government, provides recommendations on the long-term success of the life sciences sector. It was written in collaboration with industry, academia, charity, and research organisations. The report is organised into seven themes: Health Advanced Research Programe (HARP) proposal Reinforcing the UK science offer Growth and infrastructure NHS collaboration Skills Skills Skills Free relations pertaining to clinical trials include: Improve the relationship between the healthcare system and industry, and for these partners to work more coherently together to deliver better patient outcomes and create economic growth Bartners to work more coherently together to deliver better patient outcomes and create economic growth Bartners to work more coherently together to deliver better patient outcomes and create economic growth Create a forum for these of the increasingly mature digital. Capabilities in the NHS. Digital recruitment has already begun using Clinical Practice Research Datalink Create a forum for early engagement between industry, NHS and arm's-length bodies (e.g. NICE, medicines and bodies (e.g. NICE, medicines and healthcare products regulatory agency) to agree commercial access agreements.
2017	NHS [128]	Next steps on the NHS Five Year Forward Review	<ul> <li>This document reviews the progress made since the launch of the NHS Five Year Forward Review in October 2014. Specific steps relating to enhancing the UK's clinical trials sector include:</li> <li>Create a more fertile environment for clinical trials by enhancing the HRA, harmonising approval and recruitment processes, and streamlining bureaucracy including through the use of digital tools</li> <li>Strengthening of the science-base and clinical trials capability and the creation of an environment which enables small biotech and medtech companies to thrive and grow, and enhancement of our medicines manufacturing capabilities.</li> </ul>

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Organisation	Year	Report title	Issues identified	Recommendations
MTP Connect [30]	2017	Clinical Trials in Australia: The economic	Lengthy and highly variable site-to-site and study-to-study governance approval	Two priority areas identified for improvement:
		profile and competitive	processes which results in:	<ul> <li>white over the activities of Australia as a climical trials destination</li> <li>what activities are key to building a sustainable competitive edge</li> </ul>
		advantage of the sector	<ul> <li>Variability in start-up times</li> </ul>	in targeted areas?
			<ul> <li>Some sites being reluctant to take the lead role in a clinical trial and hence</li> </ul>	<ul> <li>Progress towards a national, single whole-of-sector system for ethics approval.</li> </ul>
			responsibility for providing ethics approval	Improve recruitment through public education about the role and benefits of clinical trials. Educate clinicians about clinical trials in
			<ul> <li>Some sites not processing ethics reviews in parallel with governance</li> </ul>	their area or field of expertise. Leverage the rollout and potential of electronic medical records. Link EMRs across districts and states
			applications resulting in lengthy trial	making patient records available to trial sites looking to recruit.
			start-ups	Establish sufficient capabilities and expert capacity in trials involving
			<ul> <li>Complex and variable clinical trial costing resulting in high per-patient</li> </ul>	novel design types, components, translational medicine and proof of concepts.
			costs ,adversely affects Australia's	Enhance transparency and visibility of the clinical trials sector.
			outlook as a trial destination.	How can the sector track activity and performance more consistently
			Lirrited capabilities and tolerance for high risk or innovative trials leading to	to accurately assess the state and improvements of initiatives over time and national clinical trial matric tracking? Achieve complete
			difficulties in establishing a sustainable	coverage and improved data quality in activity tracking. Options
			competitive advantage.	include expanding national reporting of statistics across jurisdictions,
			Education and training and development of competency frameworks for research	sponsor types and trial sites or alternatively, a general ethics mandate for all trials to register and undate entries on AN7CTR
			governance officers.	Challenges to be resolved in any implementation design are
			Patient recruitment.	the mandate for complete entries and incentives for updating should
			Collaboration across clinical trials	be the same throughout a trial, and data linkages and IT system
			networks.	differences between jurisdictions. Clinical trial coordination units and
			Metrics.	cross-jurisalctional working groups may have an important role to play in specialised data collection, linkage and analysis.
			Supporting infrastructure and capability for clinical trials.	Specific steps also needed to address instances where data gaps
				or lack of data fields are limiting the ability to describe or track trial artivity for the ranidly growing medical device sector Jumlement
				the systematic collection of key performance indicators and metrics
				measuring the level of benefits flowing to the sector. Priority metrics
				cover performance (trial activity, trial start-up time (including ethics and site annroval) number of participants artual vs fargeted
				recruitment, recruitment timeline – time from first patient in to last
				patient treated.

Table 10: Australian reports and reviews into clinical trials and medical health research

			ושמפש ומכוורווובת	Kecommendations
				Also economic activity (expenditure – industry, non-industry/NHMRC funding). Employment (trial sponsors/industry, trial site/clinical). Potential future sources/data-collection methods include NAS via public and private HRECs and standardised approvals; ANZCTR – expanded HREC requirements for registration and improvements in data cleaning. NAS and extension to private sites.
Australian Government, Department of Education and Training [151]	2016	2016 National Research Infrastructure Roadmap	Regulatory environment- the fast tracking of clinical trials, medical device development and access to government data were identified as being hampered by the regulatory environment. Standards and accreditation – National research infrastructure facilities need to be encouraged to undertake accreditation or certification. This should be included as part of the planning and identified in annual business plans.	Improve efficiency of clinical trials. Formal, national or international, accreditation and certification for facilities and services is critical to fostering greater engagement with industry and other end users of research. Certification and accreditation recognises the standard provided by the research infrastructure facility and demonstrates that the products or service meets specific standards. For some industries, such as health and medical research and development, certification is a legal or contractual requirement.
NHMRC [152]	2015	Clinical trials ready	What would signal that Australia is clinical trials ready?	Governance and ethics-approval procedures are efficient, reliable, timely and predictable, including: accepting single ethical review. Internal and external communication is effective, accurate and responsive. Standards and quality assurance/quality control processes are clearly defined. Participant recruitment is effective, efficient and predictable. Staffing levels are adequate, and staff have appropriate expertise, qualifications and experience. If systems and software are efficient and effective. Site uses a standard set of template documents that are agreed between sites and sponsors. Sites publish information on capability, performance and activity. Research is seen as core business of the organisation. A demonstrable clinical trials track record (in both quantity and quality). Clinical trials costs and overheads are transparent and clearly stated.

Organisation	Year	Report title	Issues identified	Recommendations
Roche [32]	2015	Clinical Trials in Australia	Inconsistent trial costs. Fragmented and variable ethics and governance process. Patient recruitment. Fragmented IT systems and paperwork requirements – inefficient, inconsistent and manual, variability and incompatibility between states and sites.	Establish a national clinical trials office-a statutory body with buy-in and involvement from health and industry portfolios at both state and federal levels. Standardisation of templates, systems and processes, and governance officer job descriptions to ensure that ethics and governance approvals are fit for purpose and efficient. Site accreditation to promote adherence to best practice and timelines. National clinical trials portal to increase awareness among patients of the existence of clinical trials and provide the opportunity for earlier access to new treatments.
NHMRC [152]	2015	Report of a national consultation. <i>Clinical</i> <i>Trials Ready: An NHMRC</i> <i>concept to recognise</i> <i>clinical trial sites that</i> <i>are 'ready' willing and</i> <i>able' to conduct clinical</i> <i>trials</i>	<ul> <li>The NHMRC had identified the need to:</li> <li>Streamline research ethics and governance approval</li> <li>Improve training and education of clinical trial proponents</li> <li>Increase recruitment into clinical trials.</li> <li>An NHMRC initiative called 'clinical trials ready' was developed in response. The initiative involves the recognition of clinical trial sites, including public and private hospitals and other organisations that are 'ready, willing and able' to carry out high-quality clinical trials in a timely, transparent and efficient manner. The proposed potential benefits of the clinical trials ready initiative were:</li> <li>Improved awareness, transparency and clarity</li> <li>Less duplication of ethics and governance review processes transparency in costs and timeframes and the high quality of the research.</li> </ul>	The following is a summary of the responses: The majority of respondents considered the proposed Clinical Trials Ready initiative to be viable and likely to make clinical trial sites more attractive to potential sponsors. Most respondents were in favour of there being no restriction on which type of clinical trial should be included. The key desired characteristics of the initiative were identified as: efficient, reliable, timely and predictable governance/ethics-approval procedures; transparency of sites, costs and participant recruitment mechanisms; and that research needed to be seen as core business and embedded in the culture of the clinical trial site. Recognition as a clinical trials ready site would follow a 2-phase assessment process and would last for a fixed period of time. Recognised sites would be required to report annually to the oversight committee and publish performance metrics. There was strong support for a web-based, searchable registry of recognised sites. Similar, existing overseas schemes were cited e.g. UK (UK-CRC), and the US-based Alliance for Clinical Trials Unit Network (UK-CRC), and the US-based Alliance for Clinical Research Excellence and Safety (ACRES) Site Accreditation and Standards Initiative (SASI). The majority view was that the initiative should be a transparent process, managed by the NHMRC, with an expert oversight body to advise on the development, training and quality standards improvement. Several respondents also proposed that research be included as one of the National Safety and Quality Health Service (NSQHS) Standards.

Organisation	Year	Report title	Issues identified	Recommendations
				General consensus that institutional support for the scheme would be essential for its success. Activities proposed as a means to demonstrate institutional support included: management support for clinical trials; education for institutional executives on clinical trial requirements; a dedicated research office/clinical trials unit; secure employment for site staff with proper classifications; funding of clinical trials initiatives; support from state/territory health departments; and a person/team at each site responsible for monitoring conformance to the Clinical Trials Ready criteria. Respondents agreed that the Clinical Trials start-up costs and
				times, to ensure an appropriate return on investment.
Australian Government Department of Health [33]	2015	Analysis of recently conducted clinical trials- final report	Costs of conducting clinical trials in Australia and lack of standardised clinical trial costs. Patient recruitment. Lengthy ethics and governance approval processes - no national system of ethics and governance processes. Poor research infrastructure and accountability.	National system of ethics and governance processes. Standardised format and templates. Parallel ethics and governance process. Standardised trial costs.

Organisation	Year	Report title	Issues identified	Recommendations
Health Consult for NHMRC [153]	2014	National consultation on a good practice process for the governance authorisation of clinical trials	Need for improved efficiency in ethics and governance processes. Inter-jurisdictional variation in standards, protocols and requirements regarding governance. Identification of legislative barriers to full implementation of National Mutual Acceptance scheme.	National ethics and governance processes but with enough flexibility to accommodate the specific nature of some trials (e.g. low-risk non- drug trials; high risk paediatric studies). Nationally agreedor standard frameworks, systems, training, education, documentation. Ethics and governance processed concurrently. National accreditation scheme for sites to be accredited as 'research mature' and able to perform clinical trials.
			Clarification and agreement on the roles and activities for individuals and entities involved in clinical trial planning and	Communication plan/map – who communicates what and when? Plus timeframes and/or benchmarks for key steps in the site-governance process.
			preparation process. Need to improve the understanding of why clinical trial research is important – to workforce, patients, health system.	Build a research culture in the healthcare sector by behavioural and organisational change– 'Research is core business'.
			Need a skilled competent and sustainable research management workforce to support a timely, efficient and high-quality process.	
			Lack of funding for research governance officers leading to under-resourcing.	
			Public hospital revenue stream from clinical trials to fund RGO positions has been decreasing as the number of trials has decreased.	
			Public hospital budget for research infrastructure eroded due to budgetary constraints.	

Australian Clinical 2014 Report on the 20 Trials Alliance [154] National Summi Investigator-Initi Clinical Trials Ne	2 2014 La imit of Cl initiated K <sub>i</sub> Networks n <sup>i</sup>	andscape of clinical trials in Australia.	Make research outputs a key performance indicator for hospitals.
	ΩŠ	linical trials and the health system. ey role and potential of investigator etworks and public-good trials. upporting a highly skilled clinical trials orkforce.	Improve the quality of routinely collected data and facilitate linkages to research databases. Expand clinical registries to collect risk-adjusted outcomes data across a broad range of high-cost, high-significance areas of medicine. Advance local expertise in trial methodology.
	ς Ω >	crategies for increasing our capacity to onduct high-impact public-good trials ithin the Australian healthcare system.	Incorporate trials within clinical quality registries. Link networks to conduct more cross-discipline trials. Coordinate and share resources and expertise between clinical trials networks (e.g. outcome measurements, data safety monitoring boards,
			education for researchers). Abolish the need to gain approval from multiple ethics and governance committees to conduct multi-centre trials. Standardise common trial dorumentation
			Move to a regulatory framework that is proportionate to the additional risk for people participating in public-good clinical trials.
			Develop an appropriate model of consent for comparative effectiveness studies when these involve widely used and approved therapies.
			Liaise with the Independent Hospital Pricing Authority to develop an appropriate costing framework for investigator-initiated clinical trials. Develop models of partnership with international investigators and funding agencies to conduct large-scale pragmatic trials.
			Develop models of partnership with industry to both conduct clinical trials and improve the competitive environment for conducting trials in Australia.
			Increase public awareness of the purpose and importance of clinical trials and increase public support through major educational campaigns.
			Conduct 'research on research' to demonstrate and understand what it is we do currently and how it can be done better, and how it affects healthcare outcomes.
			Develop effective models of consumer engagement in clinical trials. Advocate widely for the health and economic benefits of clinical trials
			and clinical quality registries to support a self-improving health system.

Organisation	Year	Report title	lssues identified	Recommendations
Australian Government, Department of Health and Ageing [37]	2013	Strategic Review of Health and Medical Research (The McKeon Review)	Research generally undervalued and poorly managed in the hospital system. Resources provided to hospitals predominantly focus on immediate consumer needs. Research viewed as an added cost. Funding originally earmarked for research in hospitals typically used to cross- subsidise other services. Inadequate management controls to track research funding or outputs audited. No way to determine how much investment in HMR is undertaken in hospitals or other health service settings. Little or no auditing of research time expended, outputs or outcomes by professional staff in hospitals. Lack of a national HMR investment target. Sector leadership and governance is required to direct, focus, oversee and coordinate activity, drive the strategic HMR vision. Lack of evaluation of research in the health system. Lack of evaluation of research in the health system. Careater integration and embedding of research in the health system is required.	Embed research in the health system and drive research activity. Establish sector leadership and governance. Manage and refocus LHN research, implement key performance. indicators (KPIs) and monitor performance. Accreditation and funding of hospitals and LHN research should be determined in part on an acceptable level of participation in clinical research as an integral part of high-quality healthcare delivery. This should require hospitals and LHNs to report on a range of research KPIs in annual reports, including research budget and actual spending, number of staff active in research, number of clinical trials undertaken, number of consumers recruited to trials and outputs from clinical research, including outcomes for patient care. Introduce a set of competitive practitioner fellowships that provide professional research can bud the nealth services duties. Introduce a set of competitive practitioner fellowships that provide professional research capacity. Provide health professionals with the opportunity to be trained and participate in research capacity. Establish integrated health research. Build health professional research capacity. Enhance public health research. Enhance public health research. Inform policy with evidence.

Organisation Yea	ir Report title	Issues identified	Recommendations
		Decline in Australia's international clinical trial competitiveness due to:	The current level of expenditure on teaching, training and research (TTR) be understood and tracked in terms of an accounting-based system of separate reporting of each TTR item (i) so that the research
		<ul> <li>Increasing costs due to the rising relative value of the Australian dollar</li> <li>Ranid increase in clinical trial canacity</li> </ul>	component can be clearly identified and benchmarked against healthcare outcomes in individual LHNs.
		<ul> <li>of low-cost countries</li> <li>Complex, time-consuming and costly</li> </ul>	Accompanying this, the panel recommends a 10-year goal of 3%–4% of government expenditure on health research and development be adopted.
		approvars processes for entrice and governance review Lack of standardised costs for clinical	Establish and resource a leadership body to facilitate translation of research into evidence-based healthcare and policy.provide policy
		<ul><li>trial activities across Australia</li><li>Lack of access to appropriate clinical</li></ul>	advice and drive sector reforms; track and monitor HIMK investment and outcomes; and work with key organisations charged with delivering better health services.
		<ul> <li>trial support infrastructure</li> <li>Difficulty in recruiting participants driven by limited access to patients by healthcare providers and lack of</li> </ul>	Establish and encourage research organisations to evaluate performance and research outcomes of investment. Performance to be evaluated across a mix of knowledge-based outputs, research inputs. and commercial. clinical and public health outcomes.
		national patient-data infrastructure to identify participants. Non-commercial trials are underfunded despite their significant potential benefits.	Establish funded integrated health research centres (IHRCs) to integrate research excellence with healthcare service delivery and facilitate best-practice translation of research directly into healthcare delivery.
			Reform clinical trials processes to address major constraints of approval times, infrastructure, lack of uniform costing, funding and patient access.
			Accelerate clinical trial reforms:
			<ul> <li>Build on CTAG Report recommendations</li> <li>Develop an online approval workflow system for trials</li> </ul>
			<ul> <li>Enhance the consumer recruitment portal</li> </ul>
			<ul> <li>Establish 8–10 national ethics committees</li> <li>Establish a mational ethics committees</li> </ul>
			<ul> <li>Establish a national clinical trials liability insurance scheme.</li> <li>Drive a national approach to implementation of clinical trials reforms through the establishment of a national clinical trials office within the HMR leadership body.</li> </ul>
			Provide additional funding of \$50–\$100m p.a. for non-commercial clinical trials.

Organisation	Year	Report title	Issues identified	Recommendations
Biotext [155]	2012	Review of the literature on participation in clinical trials: barriers and incentives for healthcare practitioners and consumers.	Patient recruitment is one of the biggest barriers to clinical trials. Reasons for patients not participating in clinical trials include a lack of knowledge about clinical trials, practical barriers such as time constraints, costs, transport access. Health professionals cited strict clinical trial inclusion and exclusion criteria.	Improve awareness of clinical trials by providing information and avenues for access, for example websites.
Clinical Trials Action Group [31]	2011	Clinically competitive: Boosting the business of clinical trials in Australia.	Timeliness of ethics and research governance clinical trial approvals. Benefits of e-health for clinical trials. Improving patient recruitment. Level of support for clinical trials networks.	<ul> <li>Single ethical review for multi-centre human health and medical research and:</li> <li>Adoption of in-common policies, procedures and forms</li> <li>Introduce policy on clinical trials to ensure efficiency through national consistency of processes</li> <li>Adequate support structures for conducting clinical trials</li> <li>Provides an incentive to reach a 30 day calendar timeframe for both ethics and governance review for which sponsors would pay a defined additional amount to support increased efficiency</li> <li>Supports a 60-day maximum timeframe for governance review</li> <li>Supports a 60-day maximum timeframe for rethics review. The compliance with which would be a condition of ethical review processes under the HoMER initiative</li> <li>Allows concurrent review of the ethics and governance components of a clinical trial</li> <li>Allows a 'stop clock' during efficient ethics and governance components of a clinical trial</li> <li>Monitor progress of these initiatives through jurisdictions publicly reporting annual data on a timeliness of ethics and governance review - types and numbers of clinical trials in a consistent format include clinical trials as a key performance indicator (KP) when jurisdictions publicly reporting annual data on a timeliness of ethics of a provals for clinical trials as a key performance indicator (KP) when jurisdictions publicly reporting annual data on a timeliness of ethics and governance review - types and numbers of clinical trials in a consistent format include a reasonable additional public hospital CEOs</li> <li>A table of standard costs associated with public hospital CEOs</li> <li>A table of standard costs associated with public hospital CEOs</li> <li>A table of standard costs associated with conducting clinical trials be developed for all trial sons or alignment with Australian Government health reform initiatives as they are introduced. The fable should include a reasonable additional public hospital ceos</li> </ul>

Organisation	Year	Report title	Issues identified	Recommendations
				<ul> <li>Introduce policy and/or systems that allow access (both on-site and remote) by clinical trial monitors and auditors to the electronic health records of clinical trial participants</li> </ul>
				<ul> <li>Request 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</li> </ul>
				<ul> <li>The NHMRC develop a consumer-friendly web portal that includes information on all current clinical trials in Australia.</li> </ul>
				The NHMRC and Department of Innovation, Industry, Science and Research (DIISR) investigate the feasibility of creating a comprehensive and searchable web portal similar to the US-based clinicaltrials.gov that would include patient recruitment, monitoring trial outcomes, registration and reporting of trial activity and to:
				<ul> <li>Identify the clinical trial networks in Australia</li> </ul>
				<ul> <li>Facilitate national coordination and encourage collaboration across academia, clinical medicine and industry</li> </ul>
				<ul> <li>Measure performance of clinical trials</li> </ul>
				<ul> <li>Report patient data for epidemiological and clinical trial feasibility studies.</li> </ul>
				Hospital performance data around clinical trials would include (e.g. timeliness, costs of trials, participation rates, comparisons with overseas counterparts, phases of trials covered, number of patients per trial, number of employees involved in trials and their field of expertise, and the clinics engaged in clinical trials and their area of expertise).
				Hospital KPIs related to clinical trials activity and timeliness could be introduced to ensure that clinical research is a priority in the healthcare system and is supported. Once KPIs have been established in the public system. these indicators will set the accented
				performance benchmarks for Australia that will influence placement of trials in the university and private hospital sectors.

Organisation	Year	Report title	lssues identified	Recommendations
Medicines Australia [139]	2011	Keeping Clinical Trials in Australia: Why Action is Needed Now	The number of clinical trials in Australia has been declining by an average of 13% per year. The aims of this paper were to: explain how clinical trials work; why new clinical trials in the national interest to reverse this trend, and strategies to restore Australia's international reputation as a centre of excellence for clinical trials. Several weaknesses were identified in relation to clinical trials. These included: small and geographically dispersed population; comparatively higher costs of conducting clinical trials in Australia, particularly for Phases II and III trials; inefficiencies in approval processes, particularly for multi-centre trials that require approvals from each participating markets such as Eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets buck as such as eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets buck as such as eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets buck as such as eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets buck as such as eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets such as Eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets such as Eastern Europe, India and China due to cost advantages, skilled labour, larger population from emerging markets such as Eastern Europe, India	For all political parties to work constructively and collaboratively to ensure that the recommendations arising from the 2011 Clinical Trials Action Group Report are implemented as a matter of priority. The recommendations include: Improving the timeliness of 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 effects of implementing the recommendations.
Pharmaceuticals Industry Strategy Group (PISG) [156]	2008	PISG Final Report	Timeliness of ethics and governance- approval processes. Electronic health records. Patient recruitment.	Accelerate the implementation of a national streamlined system of ethics-approval processes for multi-centre clinical trials (including a national patient consent form). Accelerate implementation of relevant e-health initiatives and that EMRs implemented in Australian hospitals are compatible with industry needs for validation and access to clinical trial patients' records by clinical trial monitors, especially relating toappropriately secure access for remote trial monitoring. Establish coordinated national patient-referral networks, especially in therapeutic areas of high trial activity.

# Appendix 2

Australian reports and guiding documents identified during the search of grey literature

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# Glossary of terms and definitions

Term	Definition
Clinical trial	Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. <sup>81</sup>
Governance	Governance is a set of relationships and responsibilities established by a health service organisation between its executive, workforce and stakeholders (including patients and consumers). Governance incorporates the processes, customs, policy directives, laws and conventions affecting the way an organisation is directed, administered or controlled. Governance arrangements provide the structure for setting the corporate objectives (social, fiscal, legal and HR) of the organisation and the means to achieve the objectives. They also specify the mechanisms for monitoring performance. Effective governance provides a clear statement of individual accountabilities within the organisation to help align the roles, interests and actions of the different participants in the organisation to achieve the organisation's objectives. In the National Safety Quality Health (NSQHS) Standards (second edition) governance includes both corporate and clinical governance. <sup>82</sup>
Clinical trial governance office review	Clinical trial 'governance' is the term used for institutional review or site-specific assessment (SSA). From a broader perspective, ethics-approval forms part of the overall governance framework that ensures the compliance, accountability and transparency of research activity at a site. <sup>83</sup>
Human research ethics review	A process to explore the ethical issues presented by, and implications of, a research project. Human Research Ethics Committees (HREC) play a central role in the Australian system of ethical oversight of research involving humans. HRECs review research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines, including the National Statement on Ethical Conduct in Human Research (the National Statement 2007, updated, 2015). <sup>84</sup>
Phase I	Phase I clinical trials involve the first administration of the medicine to humans, usually to small numbers of healthy volunteers. Phase I trials determine the safety of the medicine, how it works and how well it is tolerated and are usually undertaken in specially equipped centres.
Phase II	Phase II clinical trials are normally the first trials of the medicine in patients suffering the condition for which the medicine is intended. The principal aim of Phase II clinical trials is to determine effectiveness and safety.
Phase III	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/s for which effectiveness was demonstrated in Phase II clinical trials. They also determine the nature and likelihood of any side effects.
Phase IV	Phase IV clinical trials are those clinical trials undertaken after the medicine has been approved for the treatment of a particular disease. Phase IV clinical trials are undertaken to compare a new medicine to a wider range of existing therapies and interventions, as well as to further investigate the use of medicines in the normal clinical setting of the disease as opposed to the conditions under which the trial was conducted.
Site	An institution (or group of institutions) that resource, conduct and manage clinical trials that come under one of the final research governance authorisation sign off.[1]
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. <sup>85</sup>

# List of abbreviations

Abbr	Full Term
АСТА	Australian Clinical Trials Alliance
ARTG	Australian Register of Therapeutic Goods
сстсс	Canadian Clinical Trials Coordinating Centre
CEO	Chief executive officer
CIHR	Canadian Institutes of Health Research
CRN (UK)	Clinical Research Network
CRN (US)	Clinical Research Network
СТАС	Clinical Trials Advisory Committee
CTAG	Clinical Trials Action Group
СТЕ	Clinical Trials Enterprise (US)
CTJWG	Clinical Trials Jurisdictional Working Group
CRC	Clinical research centre
CTN	Clinical trials notification
СТИ	Clinical trial unit
стх	Clinical trials exemption
DHB	District Health Board (New Zealand)
DIIS	Department of Industry, Innovation and Science
DoH	Commonwealth Department of Health
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FIH	First in human trials
GCP	Good clinical practice
HDEC	Health and Disability Ethics Committee (New Zealand)
HMR	Health and medical research
HoMER	Harmonisation of Multi-centre Ethical Review
HRA	Health Research Authority (UK)
HRC	Health Research Council (New Zealand)
HREC	Human Research Ethics Committee
ICH-GCP	International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)
IRB	Institutional Review Board (US)
ISRCTN	International standard randomised controlled trial number
KAIRB	South Korean Association of Institutional Review Boards
KoNECT	South Korea National Enterprise for Clinical Trials

Abbr	Full Term
КРІ	Key performance indicator
KRBPIA	South Korea Research Based Pharmaceutical Industry Association
LHD	Local health district (NSW)
LHN	Local health network (Aust)
MRC	Medical Research Council (UK)
MRFF	Medical Research Futures Fund
MRI	Medical research institute
NCATS	NIH National Center for Advancing Translational Science
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NIH	National Institutes of Health (US)
NIHR	National Institute for Health Research (UK)
NMA	National Mutual Acceptance
NMAJWG	National Mutual Acceptance Jurisdictional Working Group
NOCRI	NIHR Office for Clinical Research Infrastructure
OHMR	Office for Health and Medical Research
OSCHR	Office for the Strategic Coordination of Health Research (UK)
РНО	Public health organisation
R&D	Research and development
RCO	Research coordinating office
REB	Research ethics board
REC	Research Ethics Committee (UK)
REGIS	Research Ethics and Governance Information System (NSW Health)
RGF	Research Governance Framework (UK)
RGO	Research governance officer
sIRB	Single Institutional Review Board
SMART	Streamlined, Multisite, Accelerated Resources for Trials
SOP	Standard operating procedures
SSA	Site-specific approval
TGA	Therapeutic Goods Administration
USA	United States of America

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