

Appendix D International best practice literature review

This section sets out a literature review showcasing international best practice in a clinical trials and health research context. Across the international examples of best practice that we have identified, comparisons are made between:

- trials conduct, frameworks, and infrastructure
- data systems and data management
- workforce capability
- research prioritisation and knowledge translation
- inclusion and focus on indigenous peoples and minority groups
- operational guidance resources for researchers and research groups.

This literature identifies that clinical trials systems are generally complex and multi-dimensional. Some of the most well-recognised trial systems are the National Institute of Health Research in the United Kingdom, the Australian Clinical Trials Alliance in Australia, and the National Institutes of Health in the United States. Although some of these trials systems share common traits, no two systems are the same, and what works in one jurisdiction may not work (and has not worked) in others.

Insights from the review

From literature and other international examples, we have identified a series of high-level messages:

- No system is perfect, and even those that are best practice have things to work on.
- The systems in place are often complex with feedback loops and are a product of many moving parts.
- Before anything, there needs to be a strong research culture to enable funding and investment in research infrastructure.
- There must be more effective avenues for development of capability of trials and dissemination of results.
- Networking amongst all trial operators is an essential mechanism for sharing workloads, developing research ideas, and encouraging higher capability.
- Research prioritisation must be a transparent process that especially involves patients and communities.
- Uniformity and ease of access to data is key to successful sharing and collaboration.
- Research must work with Indigenous populations, culture, and identity to be successful. Non-Indigenous research methods cannot be applied to Indigenous populations and expect the same results.

The following sections provide a more detailed breakdown of the points above and make reference to literature and international evidence.

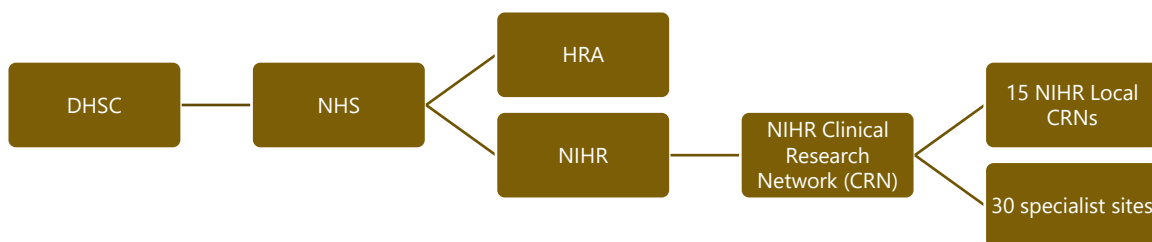
A central node to coordinate and support clinical trials activity

In international best practice it is generally seen that there is some form of central node coordinating and support clinical trials' activity within their relevant jurisdictions. Although this may be true, the way these central nodes operate and are funded varies significantly across examples.

The United Kingdom embeds clinical trials governance in the public healthcare system

The UK's clinical trials system is the result of significant Government investment, research, and planning. The Department of Health and Social Care (DHSC) is the overarching government body that funds public health care in the UK. However, it has many lower-level branches that assume different roles within the clinical trials and health research context. The figure below shows a simplification of the organisational structure of the clinical trials system. The structure is complex.

Figure 1: Funding tree in the UK in terms of health research



Source: tree generated from multiple sources of information

Directly below DHSC there is the National Health Service (NHS), a non-departmental public body funded in full by DHSC that is guided by the Health and Social Care Act 2012. It has the responsibility of day-to-day operation and funding of the public health system in the UK. There are many NHS trusts with specialist functions that make up the wider NHS system.

Underneath the NHS is the Health Research Authority (HRA), a non-departmental public body that was established in 2015 by the Health Care Act 2014. It focuses on the regulation of health and social care research, providing ethical approval and regulatory guidance.

The National Institute for Health Research (NIHR) is a virtual organisation hosted by NHS trusts, universities, and life science organisations. NIHR's focus is on clinical trials and health research specifically, and it receives funding directly from DHSC with the purpose of the advancement of clinical research in the UK. The NIHR Clinical Research Network (CRN) is embedded in the NIHR and has the two primary functions of providing clinical trials support, and awarding funding for clinical trials and research. Broadly, NIHR has the responsibilities of:

- providing facilities and people (more broadly, infrastructure) for health research and clinical trials
- providing central, coordinated management of research in the form of easily accessible data systems
- providing training and workforce development opportunities across all Local Clinical Research Networks (LCRNs)
- fostering industry relationships
- commissioning, funding, and encouraging research
- providing patient and consumer oversight
- ensuring equality of access to trials across demographics and locations for the LCRNs.

To deliver on its responsibilities, the NIHR CRN acts as a central node for 15 CRNs and 30 specialist sites within the UK at local and national levels (NIHR, n.d.-c). This is to promote uniformity in data access and data system management, efficient resource allocation and trial access opportunities, appropriate knowledge translation, and ongoing industry support.

NIHR and HRA play important simultaneous roles in ensuring successful clinical trials and health research activity in the UK. As above, NIHR's centralisation of services reduces the inefficiencies of having different, individual clinical trials systems that crowd each other out and overlap in the sense of research goals.

HRA work closely with the NIHR and the CRNs to ensure the ethical approval process for clinical trials and health research is streamlined to minimise wait times, application costs, and other inefficiency burdens. One example of how the HRA does this is through the Integrated Research Application System, which is an online, centralised application that reduces administrative duplication.

Although there are two distinctive channels in the form of NIHR and NHS, both can work together effectively, coming under the governance of DHSC and accessing the same funding pool.

The United States also has clinical trials embedded within the public health system

The National Institutes of Health (NIH) is made up of 27 specialised institutes and centres that conduct and support research across various fields of health and disease (National Institutes of Health, 2018). It is a subsidiary agency of the Public Health Service of the US Department of Health and Human Services and is the single largest supporter of biomedical research in the US. All but three of the institutes and centres receive funding directly from Congress, and it operates at a federal level.

Much like the role of NIHR, the US NIH's budget goes toward commissioning research, providing training opportunities, creating research infrastructure, and developing new research contracts. The Health Care Systems Research Collaboratory (HCSRC) is a subsidiary of NIH with the purpose of engaging with healthcare delivery organisations such as clinics and hospitals as research partners. The main goal is to orchestrate pragmatic clinical trials (PCTs) that are designed to provide real world evidence on the benefits and risks of treatment options for healthcare providers and patients (The Common Fund, 2013).

Focusing on PCTs ensures the benefits and outcomes of the research are applicable to a wide range of settings and demographics (Tunis et al., 2003). Other trials that focus too much on proving causal explanations for outcomes require exclusion criteria that are often strict. Having such strict criteria generally leads to a lower level of generalisability of results, and the likelihood of the research being meaningful and implementable for the population decreases (Tuzzio & Larson, 2019).

The US also has the Effective Health Care Program (EHC) driven by the Agency for Healthcare Research and Quality, fostering partnerships with research centres, academic institutions, health professional societies, consumer organisations, and other stakeholders (AHRQ, 2021). The EHC was established under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. The role of EHC is to facilitate and support stakeholders and partners in:

- the conduct of research
- evidence synthesis from research
- evidence translation
- dissemination and sharing of findings
- implementation of findings into healthcare.

The EHC also started receiving funding in 2013 from the Patient-Centred Outcomes Research Trust Fund to conduct and disseminate patient-centred outcomes research.

Australia's situation is very different, and the peak clinical trials body has no legislative functions

Australia's clinical trials system is quite different from the UK and US because clinical trials and health research are not embedded in the public healthcare system. Australia does not have a single, overarching government body that is responsible for national coordination or instigation of clinical trials and health research. A 2013 review of health and medical research in Australia found there was a lack of sufficiently strong connection between health and medical research and the delivery of healthcare services, suggesting this would be remedied with an embedded healthcare system (Department of Health and Ageing, 2013).

The National Health and Medical Research Council (NHMRC) was traditionally the national organisation with the function of health and medical research funding and advice for Australia. However, NHMRC's legislatively defined responsibilities, governance structure, and authority as an independent statutory agency prevent it from being an effective, overarching coordinator (Department of Health and Ageing, 2013).

Despite the lack of an overarching government health research and clinical trials system, Clinical Trials Networks (CTNs) do receive funding from governments at both the state and federal level (from NHMRC) and from public research entities, universities, and commercial sponsors (ACTA, n.d.).

In the absence of a centralised governance system, the membership-based Australian Clinical Trials Alliance (ACTA) was formed. It received seed funding from the Victorian Department of Health in 2013, and a second allocation of funding from the Victorian Department of Health and Human Services in 2016. Other primary support comes from Monash University's School of Public Health and

Preventive Medicine and financial management firm Hood Sweeney, who both assist with the operation of the alliance.

ACTA takes on the same responsibilities and roles as the likes of NIH and NIHR in ensuring a coordinated, streamlined system for data and research management services. It provides:

- insight into common issues impacting trials conduct
- collaboration opportunities between CTNs and researchers
- policy recommendations for improvement in quality of research and trials
- education and training promotion and opportunities
- strengthening of relationships between members and governments, policymakers, health care providers, industry, and consumers.

The Australian Government is currently conducting a pilot of a national Governance Framework for clinical trials and health research with the intent of outlining the governance roles at all levels of service delivery to ensure effective outcomes (Australian Commission on Safety and Quality in Health Care, n.d., 2021). The Commission are collating all data and information gathered through the pilot to assist in the refinement of the Governance Framework ahead of 2022.

Centralised governance is not a panacea; there needs to be strong leadership too

Canada's clinical trials and health research governance framework is much like that in the UK. It currently has the Canadian Clinical Trials Coordinating Centre (CCTCC) as an overarching governing body for clinical trials and health research. CCTCC provide centralised services to lower-level provincial research and clinical activity.

A summit in 2011 identified issues primarily with the ethical approval process, cost structures, and strategic organisational structures of clinical research in Canada. CCTCC was established in 2014 as a response to declining clinical trials activity nationally, with the primary intent of coordinating and streamlining lower-level provincial health research and clinical trial activity to generate operational efficiencies and make the Canadian clinical trials system more competitive internationally.

Despite the theoretical gains that could be made from having such a system, a review in 2016 established there were often cases of poor communication and coordination of CCTCC's clinical trials initiatives being undertaken at the local, provincial, and national level. As a result, there was often duplication of effort in the clinical trials and health research activity, and the potential for full system coordination had not been truly realised (CCTCC, 2016).

Although CCTCC successfully implemented several programmes that have progressed clinical trials activity in Canada, it has largely been unsuccessful in generating pan-Canadian coordination and in the streamlining of clinical trials management due to an absence of strong national leadership. At a lower level, different jurisdictions have independently strengthened their own clinical trials management systems and ethical review processes (Australian Commission on Safety and Quality in Health Care, n.d.).

Internationally peak bodies are all unique in their structure and roles

The way that health research and clinical trials are funded varies considerably across different jurisdictions and examples of international best practice. Most international examples have a range of funding sources from government, private entities, and other research institutions such as universities. Not all examples of organisations, however, have the dual function of funding clinical trials and health research, and providing a support system/network for conducting clinical trials and health research.

NIHR has a dual function in funding trials and the support infrastructure around them

NIHR receives most of their funding from DHSC, but also receives additional funding from UK Aid to support equitable health outcomes in low- and middle-income countries (NIHR, n.d.-b). DHSC provides approximately £1 billion GBP annually to NIHR to spend on health research and clinical trials (NIHR, n.d.-e).

Generally, NIHR Local Clinical Research Networks (LCRN) employ a funding model that allocates funding to the 15 local CRNs to ensure the LCRNs can adequately support clinical trials and health research at a regional level. This funding model aligns with the operational obligations specified in the NIHR Briefing Note for both the CRN and CRN High Level Objectives. The CRNs are then responsible for using the funding for supporting clinical trials and health research.

The model was simplified significantly in the 2019/20 financial year with the funding basis agreed to be unchanged until review in 2021/22 (NIHR, 2020). The 2020/21 funding allocation was awarded in three components:

- core component, made up of a fixed and variable element
- top-sliced component
- Excess Treatment Cost (ETC) Service Funding.

Fixed and variable funding

The core component of funding is a two-part model which has both a fixed and variable element. The fixed component made up 80% of the core funding and used 2018/19 allocations as a baseline for calculation. Using this baseline provided a lower-bound reference point for LCRNs and allowed them to plan their 2020/21 research activity effectively (i.e. LCRNs will know the minimum amount they can receive).

The variable component calculation is more involved but designed to incentivise LCRNs to align their proposed research activity with DHSC's strategic initiatives and objectives. For example, if a LCRN's research did not align with DHSC's strategic initiatives and objectives, it would receive a lower amount

of variable funding allocation.¹ The more the CRNs proposed activity aligned with DHSC's objectives, the more funding they received from the variable allocation.

The variable funding allocation is calculated based upon LCRNs performance against five specific metrics, each worth four percentage points of the total 20 per cent allocation. These are:

- the number of participants recruited into NIHR CRN Portfolio Studies
- the proportion of commercial contract studies in the NIHR CRN Portfolio delivering to recruitment time and target
- the proportion of non-commercial studies in the NIHR CRN Portfolio delivering to recruitment time and target
- specialty objectives, which included a range of specific areas of study (e.g. cancer, gastroenterology, ophthalmology, etc.)
- local health needs targeting, for the likes of asthma, cancer, dementia, diabetes, mental health, etc.

NIHR then uses a balanced scorecard approach, which awards points to LCRNs dependent on their performance and how they matched against the criteria (considering the complexity and volumes of the objectives). The better the performance of the CRN, the higher the score they were awarded and therefore the greater the variable allocation they were awarded.

Top-sliced component

The top-sliced component of funding for CRNs provides for national NHS service support functions and CRN National specialty leads. This is deducted from the total CRN allocation prior to the core fixed and variable elements being calculated.

ETC service funding

The ETC service funding has the function of providing additional staff resource to support the management of ETCs.

A cap and collar system is also employed to avoid major fluctuations in year on year funding. There was a 5% cap and collar, meaning that funding could only decrease or increase by a maximum of 5% from the last year's funding allocation. This ensures that the NIHR infrastructure is stable and allows LCRNs to plan more effectively.

NIH is similar in that it funds trials as well as the support infrastructure

NIH invests approximately \$41.7 billion USD annually in medical research. Of this, over 80 per cent is allocated to outside researchers mostly through competitive grants. Approximately 10 per cent of the NIH budget is allocated to projects conducted by NIH's own scientists and laboratories. The other financial support is provided in the form of cooperative agreements and contracts for research and

¹ In saying this, CRNs still received some level of allocation from the variable funding pool even if they did not match well with DHSC's strategic objectives.

research-related activities such as training, career development, resource, construction, and conferences (National Institutes of Health, 2020).

Grant funding is allocated by 24 of the 27 institutes and centres (ICs) that make up NIH. There are two levels of prioritisation of health research and clinical trials with respect to government funding:

- The first level of prioritisation is the allocation of funding to the different ICs. This is dependent on the President's priorities that can be derived from the President's Budget in each financial year once appropriated by Congress and signed into law (National Cancer Institute, 2022). Once the ICs have received their funding, the director of each IC decides which clinical trials and health research grants it will fund after considering:
 - staff input
 - scientific peer review of the grant application
 - public health need
 - scientific opportunity
 - need to balance its scientific portfolio.
- The second level of prioritisation occurs at a more detailed level within the wider areas of research. Each IC has a specific area of research regarding disease, organ system, or stage of life and therefore have individual priorities and preferences that dictate their grant allocation.

One of the ICs within NIH is the National Center for Advancing Translational Sciences (NCATS), which receives direct funding allocation under the annual budget appropriation. It was established in 2012 with the intention of improving the translational science process within the US healthcare system to ensure patients were being delivered new treatments and cures faster and more effectively (NCATS, 2015). It functions by:

- developing and demonstrating the usefulness of new approaches, technologies, resources, and models
- disseminating data, analysis, and methodologies to the research community and wider public.

Ongoing allocation of funding to departments such as these that have the core objective of advancing translational research and make it easier to implement frontier research likely contribute to better health outcomes for patients.

ACTA does not fund clinical trials directly, but supports the system around them

ACTA does not receive the same level or source of funding as NIHR and NIH due to it being a non-governmental body (i.e. it is not embedded within the public healthcare system). In 2017, ACTA received \$5 million AUD from the Medical Research Future Fund (MRFF) to support its operation in improving patient outcomes and advancing evidence-based healthcare (ACTA, n.d.).

ACTA does not directly fund clinical trial activity in Australia. However, it does support the system around clinical trials to ensure they are undertaken effectively and efficiently.

There should be a clear, logical research prioritisation framework

Research prioritisation models are important in allocating scarce resources to research deemed to have the highest value. There become problems, however, when research is not prioritised in a way that benefits the key stakeholders of the research itself, such as carers, patients, healthcare workers, and populations whose needs are generally neglected by public health systems.

At a high level, there needs to be a clear, logical process for prioritisation of research that is consistent in its assessment of potential topics and in consultation with key stakeholders. Additionally, there must be transparent, consistent, and detailed reporting of the process to maximise the success of health research and its reflection of the health priorities of the community it serves.

The suggested REPRISE guideline for reporting of research priority setting (Tong et al., 2019)

A good priority setting model for health research should be legitimate, fair, informed by credible evidence, transparent, and involve a wide range of stakeholder groups (Tong et al., 2019). Previous systematic reviews of health research priority setting have found reporting to generally be sub-optimal and extremely variable in both frequency of reporting and in the details shared.

To ensure health research is reflective of priorities and is effective, stakeholders must be able to observe the priority setting process and perceive it to be fair, legitimate, transparent, and representative of the wide range of views and priorities of the population. Tong et al. (2019) propose the REPRISE guideline for reporting health research priority setting when consulting stakeholders.

The REPRISE guideline proposed has 31 reporting items, covered by 10 higher-level domains:

- Context and scope
- Governance and team
- Framework for priority setting
- Stakeholders or participants
- Identification and collection of research priorities
- Prioritisation of research topics/questions
- Output
- Evaluation and feedback
- Implementation
- Funding and conflict of interest.

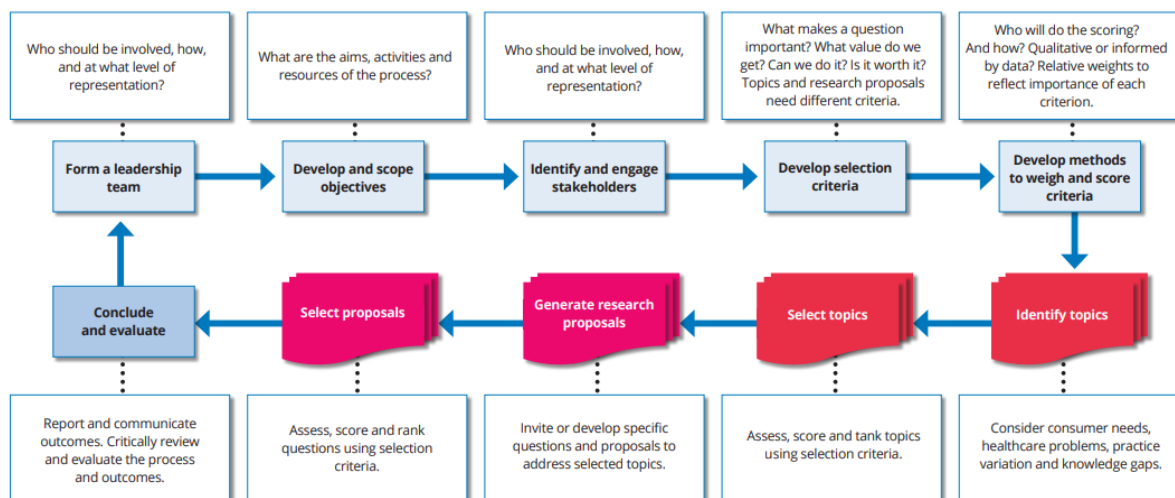
The REPRISE reporting framework ensures that those involved in the research prioritisation process have clear guidance on the required actions to take (i.e. like a checklist), and that those not directly involved in the process are able to clearly and transparently see the logic process of the research prioritisation and provide input.

The existing ACTA Research Prioritisation Framework is adapted from Nasser et al. (2013)

The ACTA Research Prioritisation Framework (2020) is a document published to explicitly outline good practice in terms of making sure meaningful, pragmatic research is being prioritised within research funding situations. The document is modelled from a paper published by Nasser et al. (2013) that aims to develop and pilot an equity lens that could help researchers in developing a more equity-oriented approach toward priority setting.

Although not mandatory to follow, the Framework provides useful resource for CTNs and funders to use in a range of settings and may help the prioritisation process for those previously unable to do it effectively. The Framework has ten stages in the priority setting exercise that effectively creates a roadmap for networks and funders to follow when deciding where to invest money and what trials should be undertaken. The figure below shows the flowchart (adapted from Nasser et al. (2013)) intended to make the prioritisation process clear, transparent, effective, and efficient (starting by forming a leadership team).

Figure 2: ACTA Research Prioritisation Flowchart



Source: (ACTA, 2020)

NIHR’s Adding Value in Research model has a similar approach to ACTA

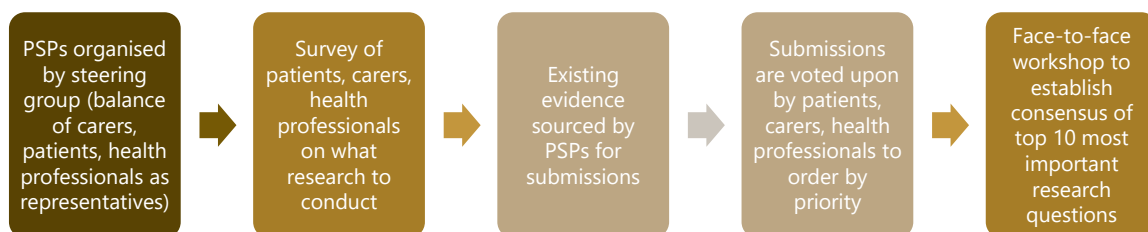
The NIHR in the UK has developed the Adding Value in Research model to ensure health research answers the most important questions and is unbiased plus designed, delivered, published, and disseminated effectively. The current version of the model has been developed over time from the 2009 work of Sir Iain Chalmers and Professor Paul Glasziou on avoidable waste in research, as well as the Lancet series on increasing value and reducing waste (NIHR, 2021).

There are five core pillars of the model that - if successfully met – should prop up a health research system that adds value to patient outcomes. These five pillars are:

- Setting justifiable research priorities
- Ensuring design, conduct, and analysis are robust and appropriate
- Regulation and management of research conduct proportionate to risks
- Complete information on methods and findings are accessible and usable
- Findings are appropriately and effectively disseminated.

The overarching model is set to make health research effective in every state, from topic establishment to application in healthcare. At a lower level, to set justifiable research priorities there is the James Lind Alliance (JLA) that brings patients, carers, and health professionals together in Priority Setting Partnerships (PSPs) (Wright et al., 2019). The diagram below shows how the process evolves in a clearly defined, linear way to prioritise research and develop consensus.

Figure 3: Process for prioritisation of research topics



Source: adapted from NIHR research priority setting web page (Wright et al., 2019).

Numerous other models have been developed and used in health research priority setting

There are numerous other research prioritisation models that have been developed to try and improve equity of health outcomes and ensure the process is transparent, logical, and involves key stakeholders.

The Council on Health Research for Development (2000) published a research prioritisation framework based on the Essential National Health Research (ENHR) strategy formed in 1990. The three base principles of the strategy and the subsequent prioritisation framework are:

- put country priorities first in research
- work for equity in health
- link research to action for development.

There are a range of steps required to effectively meet these principles that are outlined in the prioritisation framework.

Another cited research prioritisation framework is from the Child Health and Nutrition Research Initiative (CHNRI) (Rudan et al., 2008). It has 15 steps and follows similar steps to the other

prioritisation frameworks identified, using multi-criteria decision analysis (MCDA) and priority scoring to logically and ordinaly rank research options given the set criteria to inform funding decisions.

Abma and Broerse (2010) developed the Dialogue Model that focuses on increased and continuous collaboration with patients to inform health research priorities. The model was formed through an iterative validation process and applied to seven case studies across numerous different health conditions and settings. The flow-chart below shows the general process of the Dialogue Model, and how it focuses on patient involvement in priority setting.

Figure 4: General process of the Dialogue Model (Abma & Broerse, 2010)



Knowledge translation relies on coordination between all other facets of trials conduct

The Canadian Institutes of Health Research formally define knowledge translation as a dynamic and iterative process, including the:

- Synthesis, dissemination, exchange, and ethically sound application of knowledge to improving health.
- Provision of more effective health services and products.
- Strengthening of the healthcare system (Straus et al., 2009).

An effective clinical trials system facilitates the translation of knowledge between the health research community and public and implements research findings in an efficient and meaningful way to improve health outcomes of patients.

Cumpston et al. systematic review shows the key concepts for implementation of findings

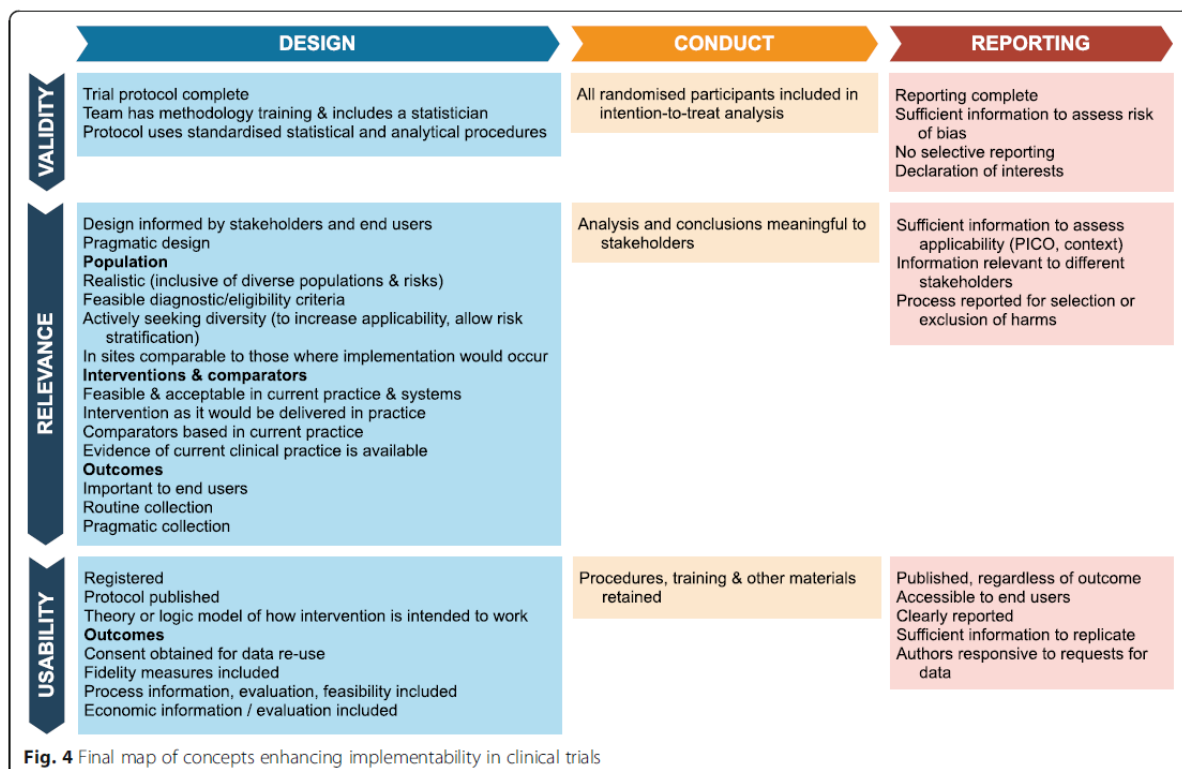
Cumpston et al. (2021) conducted a systematic review of research strategies and commitments to knowledge translation in research design and conduct. The goal was to assess the ‘implementability’ of trials as they were designed and conducted (i.e. the likelihood and ease of application of evidence from research in real-life healthcare settings) and generate an output summarising the key concepts of knowledge translation.

The systematic review process looked at English-language documents from 2009 onward that met a certain set of criteria and either related to the design, conduct, and reporting of late-stage trials, or described factors that increased or decreased the capacity of trials to be implemented. These documents came from numerous organisations, such as NIHR, NIH, PCORI, NHMRC, Canadian Institutes of Health Research (CIHR), Agency for Healthcare Research and Quality (AHRQ), and Cochrane Library. In total, 157 records were identified as potentially relevant. After initial scanning and relevance checks, 65 were used for analysis. The results were displayed in the concept map (figure below) that highlights the 38 key concepts covering:

- validity
- relevance and usability across the design
- conduct and reporting of a trial.

Importantly, no single resource identified covered more than 10 of the concepts within the map.

Figure 5: Knowledge translation concept map from Cumpston et al. (2021)



Source: (Cumpston et al., 2021)

The horizontal axis of the concept map shows the natural, progressive timeline of health research and clinical trials from design through to conduct and then reporting. The vertical axis shows the progression from validity to relevance and then usability. This is in terms of what the documents entail, and how they work towards 'implementability' of the findings of clinical trials into day-to-day healthcare.

A high-level summary of the 38 points in the concept map is as follows:

- The trial process must be complete, accurate, and well-documented.
- 'Implementability' of trials is dependent on the relevance and wide-spread applicability to populations of interest (i.e. pragmatic).
- Transparency and access to findings, methods, and data are key for being able to apply findings to a wide range of scenarios and fast-track implementation.

Translation-specific mechanisms in international best practice

In some jurisdictions there are specific bodies and mechanisms put in place to aide translation of research into practice. The two examples below are not exhaustive or entirely representative of the potential mechanisms in place globally to promote and drive translation, however, provide some reference.

New South Wales Office for Health and Medical Research

The Office for Health and Medical Research (OHMR) in New South Wales, Australia, has many functions, including the provision of training and support for commercialisation of medical devices. OHMR has a partnership with Cicada Innovations who specialise in supporting technological innovations (Department of Health, 2019). Effectively, this service lowers the barriers for medical technology companies to get their product to market and likely has flow on benefits for patients' health outcomes.

NIHR Applied Research Collaborations (ARCs)

The NIHR ARCs support applied health and care research that is relevant to the needs of local populations and health and care systems. In the UK there are 15 ARCs; partnerships between NHS providers, universities, charities, local authorities, Academic Health Science Networks, and other organisations that also undertake implementation research. The purpose of the ARCs is to increase the rate at which research findings are implemented into practice (NIHR, n.d.-d).

The research that is undertaken by the ARCs is generally dictated by what is highlighted in the NIHR *Futures of Health* report which covers the challenges of an ageing population, multimorbidity, and the increasing demands placed on health and care systems (Corbett et al., 2018). Different ARCs have different priority focuses.

Western scientific trial design and conduct must accommodate indigenous populations, not the other way around

Indigenous and minority involvement in clinical trials is necessarily placed at the forefront of an effective, equitable, and sustainable clinical trials system. In the context of Aotearoa New Zealand this means providing culturally safe, respectful, and indigenous- and minority-designed trials and research for Māori, Pacific, and rural peoples.

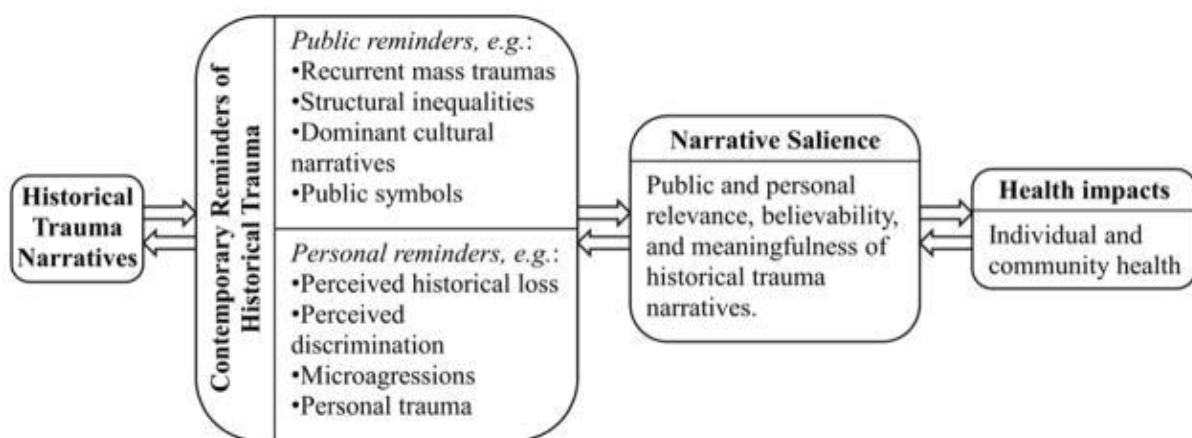
Colonisation’s impact on indigenous health outcomes is long-lasting

Settler colonialism, or the act of colonists settling and displacing indigenous populations, is recognised specifically as a factor in indigenous ill-health and disadvantage in areas of the world such as South America (Maldonado-Bouchard et al., 2015).

Current research on the effects of colonisation on indigenous peoples makes use of few specific constructs (with one main one being historical trauma) because it is generally hard to measure the relationship between colonisation and indigenous health outcomes with statistical modelling or quantitative analysis, as there are many factors in play (Axelsson et al., 2016). Despite this, the majority agree colonisation has had broad and harmful impacts on indigenous cultures (Axelsson et al., 2016).

The focus of historical trauma is largely on individual symptoms such as mourning, survivor guilt, rumination and intrusive cognition/emotion, vicarious impacts on children via parents ‘re-living’ experiences, and indirectly through impaired parenting practices (Evans-Campbell, 2008). Historical trauma has been found to impact on health over-and-above present stressors such as family violence, marital problems, or other major life stressors (Walls & Whitbeck, 2011). The figure below provides a Narrative model of how historical trauma from colonisation can impact the health of indigenous peoples currently.

Figure 6: Narrative model of historical trauma’s impact on current health for indigenous peoples



Source: (Mohatt et al., 2014)

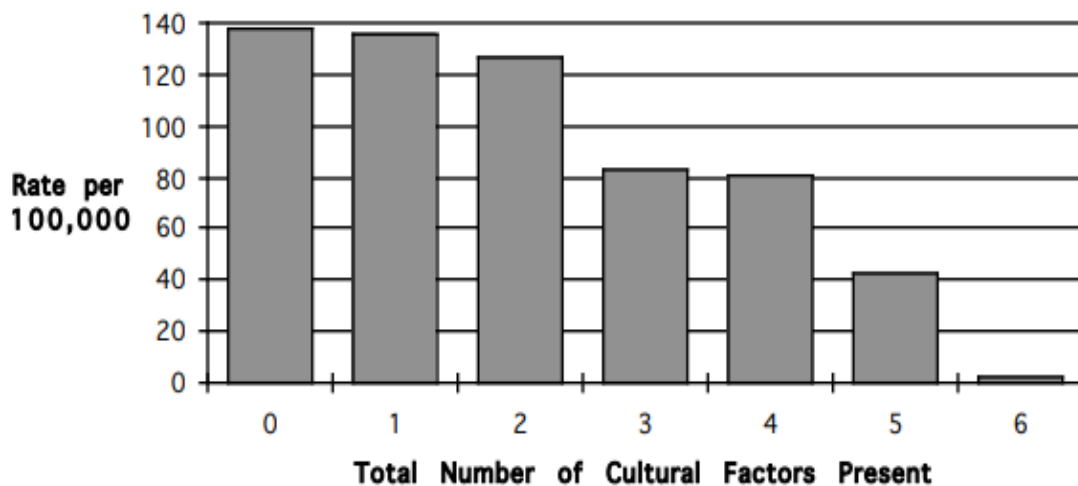
Historical trauma because of colonisation, racism, discrimination, and harassment diminishes the likelihood of indigenous populations developing trusting relationships with healthcare providers (Browne et al., 2011; Cameron et al., 2014; Denison et al., 2014; McGibbon et al., 2014). In the context of clinical trials, this may pose as a significant barrier to indigenous involvement and may further perpetuate health outcome inequities.

Decolonisation of health care to improve equitable health outcomes for indigenous peoples

Decolonisation of health care refers to breaking down the power structure of Western colonial medicines and health practices; honouring the self-determination of indigenous peoples and their rights to social, cultural, and spiritual practices within healthcare to improve the health of populations (Khan et al., 2021). The agenda of decolonisation of health care is much wider than clinical trials alone, however, provides important insights into how future clinical trials activity concerning indigenous populations should operate, and what could encourage positive, meaningful experiences for indigenous populations when involved.

One poignant study looked at Canadian First Nations youth suicide rates by cultural factors in the community (Chandler & Lalonde, 1998). The cultural factors expressed were pursuit of land claims, economic and political self-governance, control over education, police, fire, and health services, and the existence of cultural facilities. The chart below shows that the suicide rate per 100,000 youths drastically decreased as the total number of cultural factors are present that work to help preserve or restore their cultures increased.

Figure 7: Youth suicide rates by number of cultural factors present in the community



Source: (Chandler & Lalonde, 1998)

In the context of clinical trials, decolonisation likely means providing indigenous populations with much greater autonomy over their involvement in the design, conduct, and integration of clinical trials in the community. Specifically, this may also include the use of treatments, interventions, and settings

that are culturally significant for indigenous peoples to build trust and meaningful relationships with researchers. Better, meaningful, and respectful relationships between indigenous peoples and researchers may improve participation, re-focus research questions to meaningful areas, and provide better health outcomes.

Successful indigenous involvement requires partnership, indigenous led, and population-driven design, and research techniques

There are some clinical trial examples that make use of the principles of decolonisation and provide more autonomy for indigenous peoples over trial and intervention design and treatment provision. These examples, however, are only indicative of the start of a much larger process of providing full autonomy and self-determination for treatments and medicines – especially those that are socially, culturally, or traditionally different to Western methods.

Glover et al. (2015) conducted a systematic review of participation in randomised controlled trials to understand the barriers and enablers for indigenous populations to partake in clinical trials across Aotearoa New Zealand, Australia, and North America. The populations defined were chosen because of their similar experiences with colonisation and subsequent health outcomes and inequities. In total, 46 unique papers from 51 retrieved records were identified and included in analysis, with a majority focusing on Native American populations. Table 1 below shows the identified barriers and facilitators for indigenous peoples' involvement across the studies.

Table 1: Barriers and facilitators for indigenous peoples' involvement in clinical trials

Barriers to involvement	Facilitators for involvement
Lack of access for Indigenous populations to clinical trials because of disadvantage or social exclusion.	Partnership and relationship building right from the outset of the research.
Distrust of or unfamiliarity with Western European research techniques, and concerns confidentiality or privacy may be breached.	Culturally appropriate study design guided by Indigenous peoples, driven by the needs of the population and traditional practices.
Problems with research materials or the procedure and inappropriateness of how health professionals contacted patients.	Employing Indigenous staff throughout the research process for consultation and partnership.
Loss to follow up due to high mobility of participants or lengthy time involved by participating in the intervention.	Targeted recruitment techniques.
	Culturally appropriate study materials and having Indigenous people edit research material.

A 2013 literature review by the Lowitja Institute and the Australian Institute of Aboriginal and Torres Strait Islander Studies looked at the key principles for effective clinical trials and health research in the

context of Australian Aboriginal and Torres Strait Islanders (The Lowitja Institute, 2013). The main findings were:

- Research must display net benefits for Aboriginal peoples and communities.
- There must be Aboriginal community control of research including design and conduct.
- Cultural sensitivity is an essential consideration to have a meaningful and effective partnership.
- There must be full reimbursement of costs of involvement to lower the barriers to participation.

Another paper by Haozous and Neher (2015) reviews literature to determine the best practice for effective clinical partnerships with indigenous populations of North America. The key findings are that health care delivery in indigenous populations must be culturally tailored to that specific community, trust and communication are critical for successful clinical relationships, and culturally congruent care emerges from collaborative relationships that recognise, respect, and honour indigenous values and worldviews.

In-community health leaders and telehealth tools could help to get indigenous community participation

For some indigenous populations, inadequate treatment methods and often relatively isolated community centres make involvement in clinical trials difficult. McDermott, Schmidt, Sinha, and Mills (2001) ran a trial in the Torres Strait and Northern Peninsula Area Health Service District in Australia to evaluate a system for improving diabetes care in remote Indigenous communities. For a lot of the care, local Indigenous health workers could effectively administer treatment in those clinical trials.

They found improvements in most clinical trial measures at most sites when the indigenous health workers who were close to the indigenous population culturally and linguistically were administering the treatment. In addition to this, there was greater continuity of care since the indigenous health workers were closer to the community and could provide ongoing treatment and support. A three-year follow up showed sustained improvements in service delivery and intermediate clinical outcomes (McDermott et al., 2003).

However, these interventions and tools must be planned carefully and used in a culturally sensitive way

Not all treatments are necessarily able to be administered by local community health workers (i.e. more involved or specialised tasks), and therefore trials must be designed specific to the situation, regarding characteristics such as:

- geography/location of the population
- populations themselves that are included in the trial
- treatment mechanism and how the population feel about it
- continuity of treatment and level of ongoing care for the population.

There should also be effort given to enabling, training, and encouraging indigenous people to take responsibility for programmes and services that affect their health and for them to work closely with existing health systems (Gracey & King, 2009). Having trained staff within indigenous communities may help to increase the success of patient recruitment and participation.

The characteristics that make indigenous primary health care practices effective could be transferrable to clinical trials settings

Harfield et al. (2018) conducted a systematic scoping review of indigenous primary health care service delivery models to understand the fundamental characteristics for success. Generally, Indigenous primary health care services are more likely than mainstream services to improve the health of Indigenous communities.

Of the initial 2599 studies identified, 62 met the inclusion criteria and were analysed. From those, the authors pulled eight major characteristics of Indigenous primary health care models. The below diagram shows that culture is central to indigenous primary health care models, with some interdependence between other characteristics such as culturally appropriate and skilled workforce, and self-determination and empowerment.

Figure 8: Indigenous primary health care model from Harfield et al. (2018)



Source: (Harfield et al., 2018)

Although this is in a primary health care setting, there are potential lessons to be learned from this for other settings. The model above reflects what other literature states; that Indigenous peoples should have control and input into how healthcare is administered, and how the conduct of the healthcare should be embedded within the community.

Similar for clinical trials, Indigenous culture should be central to trials that take place in Indigenous communities. Indigenous peoples should have self-determination and empowerment through co-design of research questions and interventions, delivery of the treatment and trial conduct, and implementation of findings into day-to-day care and life for Indigenous communities.

Haozous and Neher (2015) identified in their review of clinical partnerships with indigenous North American populations that where distance or rural location is a barrier to care and involvement, opportunities must be taken to utilise patient navigators and community health representatives and workers to ensure ongoing care and support. As well as this, they suggest taking advantage of resources such as telehealth to expand access to specialty care.

The 'iBobbly' application from Shand et al. (2019) has been tailored and designed by Aboriginal and Torres Strait Islander communities and embodies Indigenous values in the 'acceptance and commitment'-style (ACT) intervention. In addition to this, considerations were made for those with low literacy by prioritising imagery, animations, and voice-overs, and for those without ongoing internet access due to location or otherwise.

Both examples above suggest effective clinical trials involving Indigenous populations are dependent on the same characteristics and foundations of primary health care models. Specifically, they show that:

- Culture should be central to trial and intervention design.
- Lowering the barriers to participation is important, specific to the Indigenous population of interest (in these cases, specifically remote locations).
- A culturally appropriate and skilled workforce can be used in the clinical trial to help administer treatments and ensure patients feel culturally safe.

Western Australia have established a plan for Aboriginal healthcare development

The *Western Australian Aboriginal Health and Wellbeing Framework 2015 – 2030* policy document published by the Government of Western Australia maps a pathway for the future and the development of an Aboriginal health and wellbeing framework. A roadmap like this ensures actions and health interventions are well-targeted and align with the Aboriginal health strategies of the Western Australian Government. There may be valuable learnings from a roadmap like this when considering how clinical trials and equitable engagement fits in with strategic priorities and the wider health system.

The Framework focuses on the importance of cultural determinants of health and aims to promote Aboriginal perspectives as an approach to improving health and wellbeing of Aboriginal peoples (Department of Health, 2015). The identified cultural determinants of health include:

- Self-determination
- Freedom from discrimination
- Individual and collective rights
- Importance and value of Aboriginal culture
- Protection from removal/relocation

- Connection to, custodianship, and utilisation of country and traditional lands
- Reclamation, revitalisation, preservation, and promotion of language and cultural practices
- Protection and promotion of traditional knowledge and Aboriginal intellectual property
- Understanding of lore, law, and traditional roles and responsibilities.

Alongside these cultural determinants, the Framework identifies the strategic directions and priority areas for improving the health and wellbeing of Aboriginal peoples in Western Australia. The priority areas identified, and some potential actions are:

- Addressing risk factors such as alcohol and drug use, injury, physical inactivity, obesity, oral health, maternal health, etc.
- Managing illness better by improving access to health information and services, incorporating traditional healing, knowledge, and practices into service delivery, etc.
- Building community capacity by allowing Aboriginal peoples to be in control of their own health and wellbeing, improving health literacy, ensuring a range of services work with Aboriginal communities and individuals to make informed healthcare choices, etc.
- Better health systems by making a culturally competent non-Aboriginal workforce, ensuring Aboriginal peoples are engaged in programme planning, design, and implementation, integration of traditional healing knowledge and practices into mainstream health services, etc.
- Aboriginal workforce development by building the confidence of Aboriginal people to seek and access employment opportunities within WA Health, create a culturally safe and supportive work environment, develop clearly defined career pathways for Aboriginal peoples in health, etc.
- Data, evidence, and research enrichment by involving Aboriginal people and communities in the research agenda, conducting research that is culturally relevant and of practical value to Aboriginal peoples, etc.
- Addressing the social determinants of Aboriginal peoples' health by strengthening the partnerships across all stakeholders, create collaboration opportunities between local services and Aboriginal peoples, focus on cultural determinants and promote strength-based approaches, etc.

A work culture that puts research front and centre is what drives capacity and capability to do trials

To ensure many successful clinical trials are undertaken in Aotearoa New Zealand there must be a capable workforce and institutional support to promote research, professional development, and collaboration.

World leaders in clinical trials have some mechanisms to support research

Most countries we look to as international best practice (particularly the UK and US) have a wide range of opportunities and mechanisms to support clinical trials activity and the capability of the

healthcare workforce. These aid in incentivising individuals to participate in clinical trials and health research and overall lower the barriers of entry to entry by making trials more straightforward through use of standards, guidelines, and roadmaps, and more financially viable through funding allocations.

NIHR has a range of professional development resources to foster ongoing success and research culture

The NIHR Faculty has assigned leaders of the NIHR tasked with supporting and delivering health research in the UK. The Faculty also has the responsibility of training the next generation of health researchers, ensuring longevity and consistency over time (Dementia Researcher, 2018). Importantly, the Faculty has a professional development plan, supervisory arrangement, and a line of professional accountability. There are many functions that the Faculty and the wider NIHR have for promoting the development of workforce, with three of them being the:

- operation of the NIHR Academy
- promotion of use of the Clinical Trials Toolkit
- upholding the Trial Managers Network and provision of the Trial Management Guide.

The NIHR Academy is NIHR's division responsible for the development and coordination of NIHR academic training, career development, and research capacity development. It has an integral role of attracting, training, and supporting healthcare researchers and workers to be involved in translational research (NIHR, n.d.-f). The opportunities the Academy provide are broad but can be grouped into three main categories:

- Financial awards for research, academic study, and academic researcher positions at Universities.
- Career development training in mentoring and leadership, including collaborative opportunities across organisational boundaries.
- Career recognition awards, where senior investigators are given funding as leaders who contribute significantly to NIHR and the development of the workforce.

The NIHR Trial Managers Network published *A Guide to Efficient Trial Management* to serve as a pragmatic tool for clinical researchers, providing advice and guidance for all steps of the process. It details the management process of a clinical trial by giving an overview of legal and operational trial management frameworks, providing hints and examples, as well as reference to external resources to ensure that trial leaders are aware of the necessary operations and tasks for a successful trial (NIHR Trial Managers' Network, 2014). This resource ensures that anyone conducting trials is aware of best practice and the appropriate steps to take.

NIH has the Research Training and Career Development department, as well as other mechanisms to encourage professional development

The Research Training and Career Development department of NIH in the US have a similar role to the NIHR Faculty of promoting and preparing people for careers in health research. The department does this by:

- Developing and evaluating NIH policies to sustain the biomedical research workforce at all levels.

- Analysing trends in the biomedical research workforce to see what is working, and what is not.
- Studying the economics of the biomedical research workforce and associated labour market.

The department uses these environmental considerations to inform their training, fellowship, career development, and research education opportunities and provide financial grants to researchers to encourage involvement and advancement in biomedical research and clinical trials activity (National Institutes for Health, 2019).

Another mechanism the NIH has is the NIH MD/PhD Partnership Training Program, designed to promote success and development of students pursuing a future as physician-scientists in basic and translational biomedical research (National Institutes of Health, n.d.-c). It specifically provides opportunity for innovative and interdisciplinary PhD partnerships and provides access to resources unique to NIH, the NIH Clinical Research Center, and the NIH Graduate Partnership Program (GPP).

However, opportunities are underutilised without a workforce culture that fosters research

A workforce capable of successfully undertaking clinical trials and implementing the findings into day-to-day clinical care is dependent on the underlying research culture of the health system. Having ample opportunity for professional development and involvement in clinical trials is wasted if the workforce is limited in their capacity to be involved.

World leaders in clinical trials have identified more needs to be done to change the culture of research

The NIH Physician-Scientist Workforce Report (2014) recognised in the late 1990s and very early 2000s there was significant expansion in training opportunities and research capacity that was generally matched by an increase in the growth of the NIH budget. The budget growth came to a halt in 2004, and the 2013 budget appropriation was 21.9 per cent below its 2003 level after adjusting for inflation using the Biomedical Research and Development Price Index. The report also recognises the challenges that have arisen in conducting health research because of increased costs to be medically trained and educated, the growing regulatory burdens in healthcare, and the increased funding pressure and competition for medical research grants.

The *Best Research for Best Health* strategy document from the Department of Health (2004) in the UK highlighted that major changes in the NHS at the time resulted in a lot of uncertainty regarding medical academics' roles in the healthcare system, and their ability to conduct research. It identified dwindling numbers in medical academics and put it down to disincentives for research, and barriers to involvement and progression. Some of these were:

- inadequate levels and sources of funding for medical research
- historical-based allocation for funding
- barriers to collection and use of patient data
- few effective incentives to conduct research within the NHS.

Wellcome Trust report suggests the UK's research culture still has a long way to go

Despite promising steps taken forward and many mechanisms in place to create a learning healthcare system, the UK's wider research culture still has a long way to go to become part of business as usual. The Wellcome Trust published a report in 2020 that surveyed approximately 4,000 researchers and interviewed 94 others to understand their thoughts on the health research culture in the UK and whether it is as good as it should be (Wellcome Trust, 2020).

The main findings of the report are that:

- Researchers are passionate about their work and proud to be a part of the research community.
- Research culture and individual experiences vary greatly from place to place.
- Researchers feel they work best when there is collaboration, inclusivity, creativity, support, when they are given time to focus on their research priorities, and when an individual feels safe and secure in their position.
- There are intense pressures to publish journal articles, with too little value being placed on how the results are achieved and the human costs.
- Competition is becoming increasingly aggressive and harmful and has increased concerns about job security.
- Cultural problems and pressures are having impacts on researchers' health, career enjoyment, research output quality, cherry-picking of findings, and a reduction of real innovation in the sector.

Ultimately the movement toward embedding research as part of business as usual is an iterative process. There are some ways that world leaders are encouraging healthcare providers to prioritise research. In the UK, NIHR have Research Capability Funding that is only accessible to NHS organisations that partake in research, thus encouraging them to be research active to receive additional support (NIHR, n.d.-g).

Uniformity of data and the capability to use it effectively is key for success

Adequate data systems are crucial in ensuring fast, easy, and open access and management of data for those involved in clinical trials. The three key facets of data systems are the:

- Safe access to, and uniformity of, administration datasets.
- Safe access to, and use of, clinical registries and databases.
- Capability of the system in handling big data.

The benefits of fast, easy, and open access and management are mainly in improving transparency and knowledge translation from different trials for use in current and future research and clinical care.

Easy access to electronic health records allows specifically for identification and monitoring of patients and their safety, more (and better) patient recruitment opportunities, and lower trial costs through point-of-care randomisation (i.e. trials that are embedded in public healthcare service provision).

ICTRP sets the gold standard for registries data

The International Clinical Trials Registry Platform (ICTRP) was set up in 2006 by the World Health Organization (WHO) with the intention of facilitating a single point of access and the unambiguous identification of trials internationally (WHO, n.d.-a). The International Committee of Medical Journal Editors (ICMJE) required that clinical trials be registered in publicly available trials registers before they can be considered for publication (De Angelis et al., 2004).

The purpose of such a system is to ensure trial details are available to all, regardless of an individual's role within the clinical trial. The increased availability of information publicly about clinical trials (published or otherwise) may encourage improvements in trial methods, a reduction in publication biases, and increase the general awareness of research being undertaken at that point in time (Gøtzsche et al., 2006). This is ultimately important for knowledge translation and implementation of recent research findings in day-to-day clinical care.

WHO operate a high-level network called the ICTRP Registry Network which connects:

- Primary Registries
- Partner Registries
- Data Providers
- Registries working with the ICTRP towards becoming Primary Registries.

Primary Registries are those that meet specific criteria for content, quality, validity, accessibility, unique identification, technical capacity, and administration of trials. These registries specifically meet the requirements of ICMJE (WHO, n.d.-b).

Partner Registries meet the same requirements as Primary, but do not need to:

- have a national or regional remit or the support of government
- be managed by a not-for-profit

- be open to all prospective registrants.

All the Partner Registries must be affiliated with either a Primary in the WHO Registry Network, or an ICMJE approved registry.

Data Providers are responsible for a database that is used by one or more registries. They provide data to WHO for inclusion in the ICTRP Search Portal, meaning the data is publicly available if it is created and managed in a way that is consistent with the WHO Registry Criteria.

Australia and Europe have ICTRP Primary Registries

The Australian New Zealand Clinical Trials Registry (ANZCTR) is an online register of clinical trials being undertaken in Australia, Aotearoa New Zealand, and elsewhere. It was one of the first registries to be recognised by the World Health Organisation (WHO) as a Primary Registry and contributes directly to the WHO ICTRP. Having this accreditation and status is essential for keeping Australian and Aotearoa New Zealand clinical researchers connected internationally and allows for widespread sharing of information.

The European Union Clinical Trials Register is like ANZCTR, but generally focuses on trials conducted in the European Union. It is also a Primary Register for the ICTRP meaning it follows the same data protocols that are important for transparent, uniform knowledge translation and record keeping (European Medicines Agency, n.d.).

Best practices have specific research objectives and divisions of health services to promote big data proficiency

Clinical trials (and randomised controlled trials more specifically) generally have high internal validity of results for patients and settings in the context of the trial itself, but struggle to be applied more generally to populations and in clinical practice because of issues with:

- reproducibility of results outside of sample
- generalisability of the sample to routine practice
- infrequent external validation of results
- sample selection bias
- characterisation of confounding factors
- ethics
- use for rare events (Mayo et al., 2017).

Mayo et al. (2017) suggest that big data analytic resource systems have the potential to augment and extend randomised controlled trials, and may make it easier to design better clinical trials at lower cost. Additionally, standardisation of data elements, clinical processes, and reporting conventions make it easier to adopt big data systems that could allow inclusion of external clinical validation phases to clinical trial design and increase trial participation.

However, they also identify that big data analytic resource systems are generally not uniform globally, and the large volume and variety of them creates challenges technically, conceptually, and in terms of policy.

There are several good examples of research bodies that have the specific function of developing capacity and capability to use big data in clinical trials, and in advancing translational research to embed trial findings in clinical care.

NIH Common Fund Big Data 2 Knowledge (BD2K)

NIH have a subdivision called the Office of Strategic Coordination – The Common Fund. It is a component of the NIH budget that provides funding to support and answer emerging opportunities and issues within biomedical research that no one NIH institute can address on its own. One of the Funds functions is the Big Data 2 Knowledge (BD2K) programme which supports the research and development of big data systems for use in biomedical research (The Common Fund, 2021). BD2K has specifically been used to:

- build appropriate software and dissemination analysis methods to process and use complex big datasets for research
- fund, support, and encourage training for large-scale data analysis
- make datasets findable, accessible, interoperable, and reusable
- provide wider access to the research community on use of big data as well as informing the NIH Strategic Plan for Data Science.

The programme to date has successfully:

- trained over 30,000 individuals in biomedical data science
- published over 255 biomedical data science educational resources
- developed over 200 software, tools, and methods to effectively use big data
- created a data index prototype to easily find and access biomedical datasets.

Programmes such as this that have a distinct funding role in upskilling and encouraging big data use and proficiency lower barriers to performing clinical trials and could make an overall clinical trials system more effective.

NIHR Oxford Biomedical Research Centre

The Oxford Biomedical Research Centre is a subsidiary of NIHR who have research objectives for supporting the overall operation of biomedical research within the United Kingdom (Oxford Biomedical Research Centre, n.d.). One of their research themes is Clinical Informatics and Big Data, as it has been highlighted as an area of need for development in the next stages of translational research and effective utilisation of biomedical data.

This research theme became central to the Centre because effective big data use is generally expensive, time consuming, and error prone. To combat this, the Centre has:

- Established a comprehensive, catalogued data warehouse for Oxford University Hospitals NHS Foundation Trust.
- Created data products for key therapeutic areas, in collaboration with colleagues from BRC scientific themes.
- Delivered a governance framework for data processing and re-use across the university-hospital partnership.

Further, the Centre aims to:

- Establish a secure, cloud-based research data platform for the university-hospital partnership to promote safe, easy access to big data.
- Develop algorithms for research data abstraction and phenotyping in key therapeutic areas, in collaboration with colleagues from scientific themes.
- Deliver research outputs enabled by this new informatics infrastructure, in collaboration with colleagues from scientific themes.

Importantly, the Centre works closely with the NIHR Health Informatics Collaborative that has the task of improving the quality and availability of data for translational research across the entire NIHR network of biomedical research centres.

Themes and applications established by the Centre can then be extended further than just the Oxford university-hospital relationship and applied to the entire United Kingdom health system. Tangible work such as this likely makes it easier for clinical trials to be performed and for the overall clinical trials system to be effective.

University of New South Wales (UNSW) Centre for Big Data Research in Health (CBDRH)

The UNSW Centre for Big Data Research in Health (CBDRH) is the first Australian research centre dedicated to health research using big data, with the objectives of co-creating research that brings together academics, consumers, clinicians, and service and policy organisations to frame relevant research questions that are significant in real-world contexts (Centre for Big Data Research in Health, 2022).

The role of CBDRH is to operate as a hub for collaborative interdisciplinary research, methodological development, and training to do with big data research and use. CBDRH provides a unique example of a collaborative node outside of the public health system that has the purpose of upskilling the clinical research workforce and making big data easier to use.

There must also be explicit methods of dealing with Indigenous eHealth data in culturally sensitive ways

Maar et al. (2019) analysed data from the Diagnosing Hypertension-Engaging Action and Management in Getting Lower Blood Pressure in Indigenous Peoples and Low- and Middle- Income Countries (DREAM-GLOBAL) trial over a period of five years to identify wise practices for culturally safe and collaborative eHealth randomised controlled trial research with Indigenous communities.

Based on the findings, successful eHealth research in collaboration with Indigenous communities necessarily requires a focus on cultural safety and includes:

- Building a respectful relationship with the indigenous community partaking in the research and to which the research will be applicable for.
- Making effort to maintain the relationship with the indigenous community before, during, and after the research.
- Clear, consistent communication and support for the local team during the trial.

- Commitment to codesigning the innovation with the indigenous community.
- Supporting task shifting with the local team.
- Reflecting on mistakes and lessons learned or areas for improvement that support learning and cultural safety in futural health research and clinical trials.

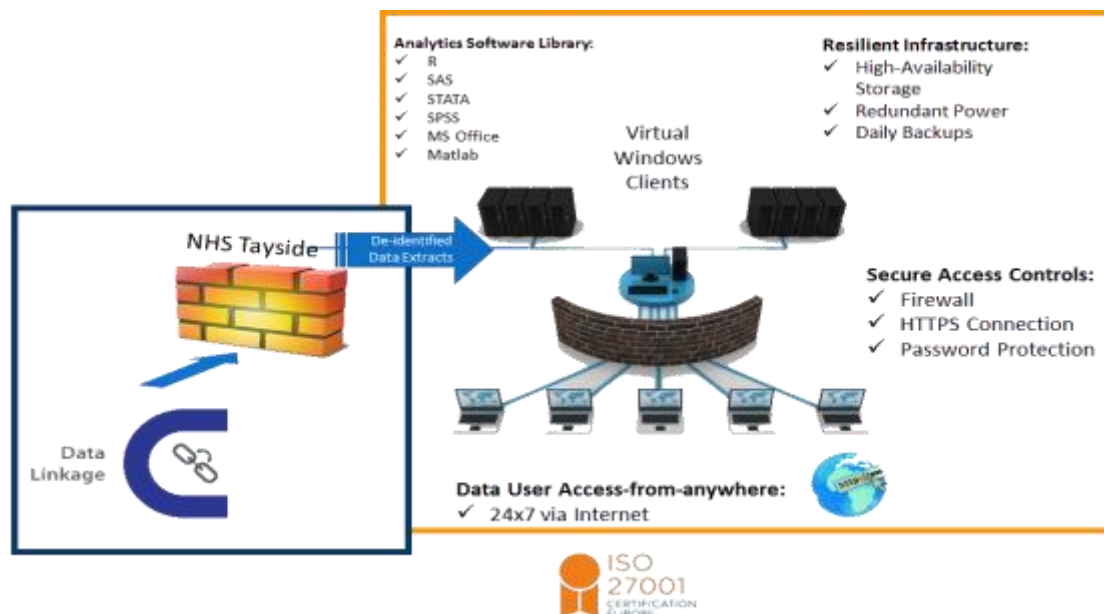
Data storage safe havens are increasingly common and effective for secure storage

Data safe havens are becoming increasingly popular and central to the facilitation of secure storage and use of biomedical data. ISO 27001 is the overarching information security management standard that most of the data safe havens covered below are built upon and accredited to.

Effectively, data safe havens provide a way for people to use sensitive data for research purposes without exposing the data to the risk of being moved around. It greatly reduces the possibility of the data (i.e. patient records) falling into a situation that may ultimately be harmful if released. Generally, users require access approval contingent on their research and never get a physical copy of the data – every act of manipulation or analysis happens remotely, plus the data never leaves the haven, ensuring a single source of truth remains.

The figure below illustrates how data safe havens generally work, and how researchers can remotely access the data from anywhere. The safety is dependent on secure access controls (firewall, HTTPS connections only, password protections, etc.) and resilient infrastructure. Researchers then also access analytical software remotely (i.e. not on their own device, but through the server).

Figure 9: Remote-access nature of data safe havens explained



Source: (University of Dundee, n.d.)

University of Dundee Health Informatics Centre

The Health Informatics Centre (HIC) at University of Dundee is a remote-access safe haven environment designed to protect data that is confidential as well as satisfy public concerns about data

loss. Data is not released to external data users for analysis on their own computers and is instead stored and analysed solely on a server at HIC within a restricted, secure IT environment. There is a process that data users/researchers must go through to become accepted and to be able to access the data facility remotely (University of Dundee, n.d.).

Once access has been gained, researchers will be able to use programmes for analysis such as R, Stata, SPSS, SASS, Matlab, and Microsoft Office.

University of Edinburgh Data Safe Haven

In its previous form, the Data Safe Haven (DSH) was a controlled and secured service environment for undertaking research using sensitive data (i.e. confidential data likely to cause harm if breached) for approved members at the University of Edinburgh. This required a range of robust controls and safeguards for the secure transfer of sensitive data into a highly secure environment where it could be stored, manipulated, and analysed by approved members of a research team (University of Edinburgh, n.d.-b).

Now, DSH is converging with another University of Edinburgh project to form the Edinburgh International Data Facility (EIDF) designed to service Edinburgh as well as South-East Scotland and others. EIDF provides long-term hosting and curation of major regional, national, and international datasets for a wide range of institutions, including academia and industry. It offers cloud-like and high-performance computing environments for big data capabilities (University of Edinburgh, n.d.-a).

Swansea University Secure Access Laboratory Safe Haven

The Swansea Secure Access Laboratory allows for researchers to enter two 'safe settings' where users securely interact with data. These two settings are at the Data Science Building at Swansea University and at Cardiff University. Researchers enter these spaces that are much like data safe havens at Edinburgh and Dundee, in that the data remains within the space and cannot leave.

These 'safe settings' ensure that only pre-approved researchers can interact with the data within the research programmes, and that confidentiality, integrity, and availability standards are upheld and in line with data provider requirements and expectations (Population Data Science at Swansea University, n.d.).

Monash SeRP

Monash SeRP is a secure environment for sharing research data for collaboration and analysis within the control and governance of a data custodian (Monash e-Research Centre, n.d.). The custodian (or designated project manager) is afforded visibility and control over how their data is being used by other approved researchers. Project owners request for projects to be created and then a data custodian is appointed who can:

- allocate controlled access to the dataset
- provide computing power and approved analytical tools to approved researchers
- manage the controls of the environment, including restricting access to the internet
- restrict the importing of data
- authorise all removals of data
- audit the usage of data and compute resources.

Approved researchers can access the data remotely and operate in a safe environment where all data and subsequent analysis stays onsite, minimising the risk of data travel and unauthorised access.

Data and statistical coordination centres provide centralised support within some contexts

There are many examples of data and statistical coordination centres internationally that play an important role in providing centralised support for data management and analysis. In some cases, coordinate centres offer a wider range of services than just data and statistical support (i.e. study design, protocol writing, etc.).

Data and statistical coordination centres generally help investigators to:

- Follow good clinical practice and principles of sound scientific research.
- Adhere to Standard Operating Procedures (SOPs).
- Collect data accurately and in a readily usable fashion.
- Monitor study data and documents for quality and accuracy.
- Meet defined quality standards or metrics.
- Produce clinical trial results that are more complete, reliable, and reproducible (Ecklund, 2016).

In most cases a data and statistical coordination centre reduces the burden on investigators to manage all their conflicting and time-intensive priorities and necessary activities throughout a clinical trial and lead to higher quality outcomes. Without assistance, this burden can lead to miscommunication, resource issues, time runouts, lack of standardisation in processes, and overall may lead to insufficient attention to detail and less-than-ideal results from the trial.

In 2011 principal investigators and staff from data coordinating centres across the NIH in the US met to develop a compendium of best practices for data coordinating centres. The compendium covers four main domains:

- clinical study/trial operations
- data management
- quality assurance/control
- human subjects' (HS) protections and regulatory affairs (NHLBI, 2011).

The compendium essentially acts as a roadmap for establishing a data coordinating centre and applying for funding in the NIH. The diagram below shows what considerations each domain covers at a high level.

Figure 10: Compendium of best practice for data coordinating centres (high-level)



Source: adapted from (NHLBI, 2011)

The Center for Clinical Trials & Data Coordination (CCDC) at University of Pittsburgh, United States

CCDC was established in 2015 through institutional funds with the goal of providing clinical trial design, conduct, coordination, and analysis expertise, as well as an opportunity for the advancement of the careers of clinical investigators and accessing large data coordinating centre grants (Abebe et al., 2019). CCDC is the result of a lot of planning, and functions as a central point of insight and guidance for clinicians wanting to access support in designing, conducting, coordinating, and analysing trials.

The centre has a bespoke clinical trial management system with nine characteristics that manage clinical trial data from conception right through to the close-out of the trial (see figure below).

Figure 11: CCDC trial management system components



Source: (Abebe et al., 2019)

The choice to develop this homegrown, bespoke model as opposed to using a pre-existing model was made because of the flexibility it provided to incorporate different, and potentially more, characteristics for the management system. This also allowed CCDC to take the learnings and strong, important components from other systems such as REDCap and tailor them to allow greater control and usability for the CCDC context.

For example, for electronic data capture CCDC use a Microsoft SQL web-based data entry system built in accordance with FDA database requirements. One benefit of this web-based data entry system is that over time CCDC have created a database of online form types for different activities (coded by number). This easy identification of form types allows for ‘study-agnostic’ forms (i.e. generalised forms) to be recycled from project to project with very little modification, overall streamlining the administration process and saving time.

In terms of statistical analysis and reporting, CCDC have statisticians that lead the analysis and a standard report template that is adapted to the specifics of each study. CCDC and the investigators work together to draft findings and once approved, statisticians enter the data into the report and present the findings with respect to CONSORT guidelines. CCDC then also manage the dissemination process.

For data sharing, CCDC has a hand in the registration, updating, and final reporting to clinicaltrials.gov, the US clinical trial registry. CCDC also maintain complete data dictionaries, format libraries, and macro libraries for datasets and other tools so that the data can be shared with NIH repositories to be re-used.

Overall, these functions (along with the other six not fully detailed) help to achieve efficient, consolidated advice and support services for clinical trials by streamlining administration processes and reducing the technical burden on investigators.

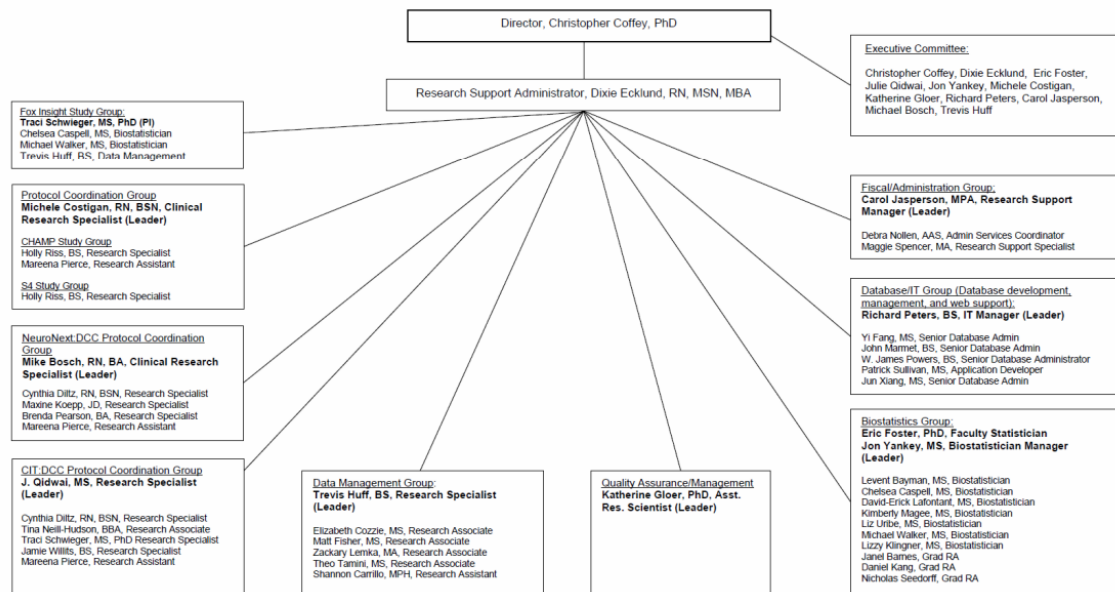
Clinical Trials Statistical and Data Management Center (CTSDMC) at University of Iowa, United States

The Clinical Trials Statistical and Data Management Center (CTSDMC) at the University of Iowa is another coordination centre with well documented establishment and purpose. CTSDMC provide centralised services for:

- Trial design, including traditional and adaptive study design, model validation, and protocol development.
- Data management and information technology, including relational database design and development, distributed data entry systems, and electronic data capture.
- Study coordination, such as clinical site support, training and certification, regulatory support, and clinical site monitoring.
- Biostatistical support through statistical analysis plan development, interim and final statistical analyses, and manuscript preparation.
- Communications and logistics, including forming communication strategies, meeting planning, and project management.
- Quality management, such as programme effectiveness evaluation, data safety and integrity checks, and compliance checks (CTSDMC, n.d.).

The following figure shows how CTSDMC operates in terms of its organisational structure. There are dedicated resources that relate and operate in line with the functions identified above (i.e. quality assurance, statistical analysis, data management, etc.).

Figure 12: CTSDMC organisational structure



Source: (Ecklund, 2016)

Improving Palliative, Aged and Chronic Care through Clinical Research and Translation (IMPACCT) Trials Coordination Centre at University of Technology Sydney, Australia

The IMPACCT Trials Coordination Centre in Australia aims to support researchers to engage with high-quality research by offering similar services to CCDC and CTSDMC in the US. The services they provide are:

- New study design and development, including protocol design, systematic and literature reviews, and sample size calculations.
- Multi-site clinical trial coordination, including site feasibility, trial registration, ethics applications, information and consent forms, SOPs, guidance documents, templates, etc.
- Data management, including REDCap databases, data collection worksheets, randomisation, data checking and planning, statistical and health economic analysis, etc.
- Safety reporting (adverse event reporting, medical monitoring, etc.).
- Site investigator and pharmacy manual development (randomisation schedules, online randomisation and unblinding, etc.).
- Investigational medical product (GMP-certified manufacture, stock ordering).
- Project management, including study budgeting and payments and budget tracking.
- Site research staff training, site initiations, consent training, and GCP training.
- Assistance with recruitment through promotional materials and consent scripting (ITCC, 2020).

Operational level guidance to promote successful trial conduct

Provision of operational-level guidance is greatly important for the success of running a clinical trial. It allows researchers to directly see best practice examples and understand the appropriate actions to take when considering the design, conduct, and implementation of trials and their findings.

Operational guidance can take many forms – from a simple document, through to centralised resources and physical services.

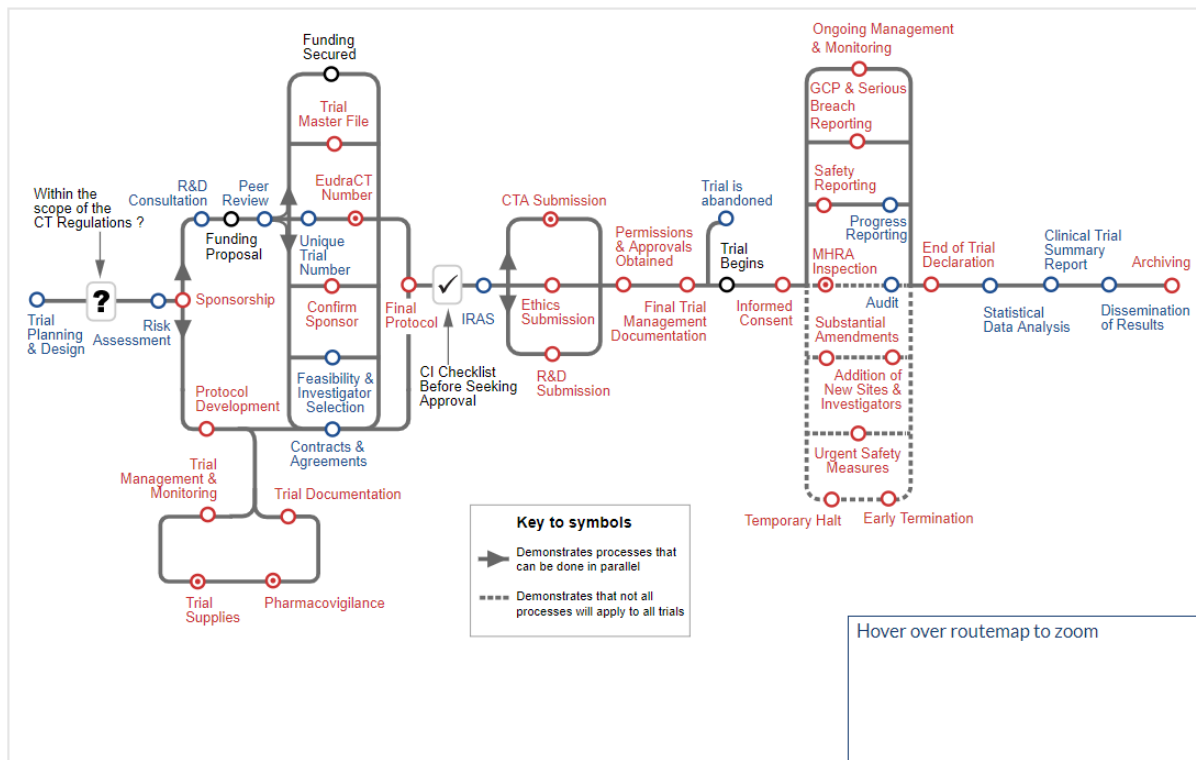
First, some high-level operational guidance resources from around the world

There are a few high-level guidance compendiums or central locations for researchers that provide general guidance information. Alone they may not provide sufficient support to get a clinical trial up and running, however they serve an important purpose of generating awareness of the right things to be considering when designing and conducting a clinical trial, as well as providing good reference to further, more in-depth resources.

The NIHR Clinical Trials Toolkit in the UK

The Clinical Trials Toolkit is a resource hosted by NIHR that provides an interactive routemap for clinical researchers to ensure all steps have been taken for successful application and conduct of clinical trials. The routemap is formulated with UK regulations and clinical good practice in mind and provides direct support for researchers navigating the clinical trials process (NIHR, n.d.-a). The diagram below shows the routemap from start to finish of a clinical trial and the involved steps in between.

Figure 13: NIHR Clinical Trials Toolkit routemap of conducting a clinical trial



Source: (NIHR, n.d.-a)

Each node on the routemap is interactive and when clicked on, redirects to an information page with important classifications, questions to ask, and links to further resources that may be helpful to researchers.

The Australian Clinical Trials Toolkit from NHMRC

The Australian Clinical Trials Toolkit is a webpage much like the NIHR's, except it lacks an interactive routemap. Similarly, it points towards overarching legislation and guidance that is necessary to consider when designing and conducting a clinical trial, as well as guidance for good clinical practice (NHMRC & Department of Industry, Innovation and Science, 2017).

The Toolkit can be broken down into three main sections of discussion:

- Planning a clinical trial, including finding a suitable site, feasibility, research governance, and applying for ethics.
- Registration of a trial, trial conduct information, and closing a trial, including safety monitoring, training, publish results, and steps post completion.
- Other resources, which points toward useful links to organisations and clinical research networks, intellectual property information, and how to foster relationships with industry.

United States has many higher-level guidance toolkits

The United States has multiple higher-level toolbox-like resource banks for clinical research that researchers can access and use as guidance. One example is that of The Interventional Studies in

Aging Center (ISAC) at the Institute for Aging Research (IFAR) which provides a comprehensive 7-part guide covering:

- Background about what a clinical trial is and what appropriate training opportunities are out there to become equipped to conduct a clinical trial.
- Experimental design and statistical considerations to be made when designing and conducting the trial.
- Human subject protection and research regulation, including outlines of relevant laws that must be adhered to.
- Essential documentations throughout the trial process, for both regulatory and efficiency and effectiveness purposes.
- Project management and how to maintain effective overview of the trial process.
- Data management and insight into how to store, use, and report data.
- Publication and dissemination for post-trial – including data sharing, selecting a journal, and other general considerations (Interventional Studies in Ageing Center, 2018).

The toolbox also points researchers toward other relevant documents that would be helpful in successfully conducting a clinical trial.

Another example is the National Center for Complementary and Integrative Health (NCCIH) Clinical Research Toolbox. NCCIH are an NIH centre and provide the toolbox webpage as a consolidated form of guidance for researchers wanting to undertake clinical trials. The website is slightly more barebones in style, simply providing external links to important references regarding the overarching areas of clinical research:

- Those relevant in the start-up of clinical research (data monitoring and safety plan, protocol templates, monitoring committees etc.).
- Documents for during the conduct of clinical research (how to amend protocols, what to do when there are unexpected problems, site screening etc.).
- On-site monitoring programme requirements (site checklists for before, during, and after a trial).
- Milestone documents at each stage of the trial.
- Additional training and resources that may be useful, such as GCP learning resources, FDA clinical investigator training, and REDCap information (NCCIH, 2022).

Canada also has some examples of general guidance toolkits

Fraser Health in Canada also have a clinical research start-up toolkit designed to point researchers in the right direction when considering the appropriate steps to take in setting up a clinical trial. Much like the NCCIH example, the Fraser Health toolkit is relatively simplistic, providing external links to templates regarding budgeting and finance, protocols for investigator-initiated research studies, regulatory binders, clinical site and study start-up things like version control and site qualification checklists, conduct of clinical research documents, and completion and close-out practices (Fraser Health, 2018).

The British Columbia Academic Health Science Network provide a slightly different guidance document, however still useful for researchers in conducting effective clinical trials. It focuses on study results best practices and how to manage the relationship with patients before, during, and after a trial. It points to relevant documents and guidance, plus offers researchers templates of communication documents to ensure patients are aware of what is going on (British Columbia Academic Health Science Network, 2020). Clinical Trials Ontario also offer similar guidance for participant experiences (Clinical Trials Ontario, n.d.).

Funding guidance

There exists a reasonable amount of guidance for funding across different jurisdictions. The guidance generally covers how to apply for funding, as well as where to find appropriate funding.

NIH Grants & Funding Center Information on Funding and Grant Applications

The NIH Grants & Funding Center provides interactive guidance explaining the funding process right from the conception of a research idea through to the application process (National Institutes of Health, n.d.-b). It effectively acts as a toolkit and central resource for all funding questions and answers, covering important areas such as:

- Finding the right fit for a research project (i.e. where does the research idea fit into NIH's strategic landscape and research priorities?).
- Who is eligible for NIH funding, dependent on the appropriate grant programme.
- The types of grant programmes that are offered by NIH, from research grants, career development awards, training and fellowships, through to centre grants.
- The types of grant applications there are (new grants, renewals, revisions, etc.).

The centre also provides detailed information on how to find funding and outlines the necessary steps to be taken in preparing, writing, and submitting applications.

NIHR Research Design Service and NIHR Clinical Trials Toolkit

NIHR provide the Research Design Service (RDS) network to health and social care researchers across England. It is a free and confidential service physical consultation service for researchers who have a research idea and are not sure how to turn it into a funding application (NIHR, n.d.-h).

The RDS provides bespoke advice on:

- Designing a study
- Research methodologies (quantitative and qualitative)
- Identifying suitable sources of funding
- Involving patients and public in research design
- Identifying potential academic, clinical, SMEs, and public collaborators
- Identifying and refining the research question
- Medical statistics
- Health economics
- Advice on common pitfalls

- Interpreting feedback from funding panels.

There are ten RDS sites across the different regional centres of England which helps to make the service accessible across the country.

The NIHR Clinical Trials Toolkit discussed earlier also provides useful funding guidance throughout the interactive routemap.

NHMRC online funding guidance

NHMRC in Australia provide some online guidance for funding for health research (NHMRC, n.d.). At a high level, it captures:

- Where to find funding (with a continually updating list of funding opportunities).
- The importance of peer review for research and funding applications, as well the guiding principles for peer review nomination and appointments.
- Managing funding streams, including involvement with the Medical Research Future Fund and varying grants, reporting, and using the NHMRC grants management system.
- The new grant programme and subsequent eligibility.
- Data on research, and the projects NHMRC have previously funded, plus the achievements and expected future outcomes of the research.
- The Medical Research Future Fund and the subsequent grant opportunities available under it.
- Opportunities for collaborative health research and other areas of potential funding.
- The schemes and calendar for funding activities from NHMRC.
- The key considerations to make in funding applications, and the support NHMRC can provide in the process.

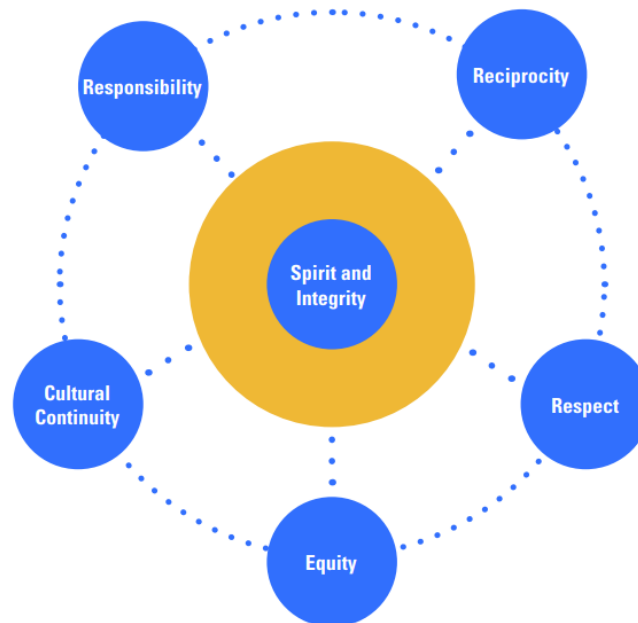
Indigenous involvement guidance documents

There are some guidance documents from around the world that detail the appropriate ways to engage with and conduct research within Indigenous communities. This showcase of guidance documents is not extensive and only covers some Indigenous populations of Canada, North America, and Australia. Additionally, not all the steps will necessarily be applicable or culturally appropriate in the context of Aotearoa, however the overarching principles of early relationship building, self-determination and research guidance from Indigenous peoples, operation in culturally safe spaces, and open and continual communication and collaboration seem to be common across guidelines.

NHMRC Guidelines for Aboriginal and Torres Strait Islander Peoples involvement in research

NHMRC have published a guideline document regarding ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities (NHMRC, 2018a). The diagram below shows the interdependence between the six core values of ethical research.

Figure 14: Six core values of ethical research with Indigenous peoples



Source: (NHMRC, 2018a)

The document explains the core values in the context of research and provides researchers and stakeholders with examples of how to demonstrate the values throughout the process. The document also provides links to relevant sections of the National Statement on Ethical Conduct in Human Research (NHMRC, 2018b).

For example, cultural continuity refers to the sense of strong, shared, and enduring individual and collective identities. Cultural continuity includes maintaining the bonds and relationships between people, and between people and their environment, as well as in respect of spiritual domains. Cultural continuity is reflected through:

- Understanding Aboriginal and Torres Strait Islander Peoples' experiences and perception of research as an exploitative exercise.
- Recognising the importance of the personal and collective bonds within Aboriginal and Torres Strait Islander communities and the critical function of these bonds in their social lives.
- Engaging with Aboriginal and Torres Strait Islander people and communities; collectively, individually, or both.
- Finding ways to work without diminishing the right to the assertion or enjoyment of cultural distinctiveness.
- Demonstrating respect for the intrinsic values-based expectations and identity of Aboriginal and Torres Strait Islander people and communities.

The examples given of demonstrating cultural continuity are:

- Negotiated participation in cultural events and the sharing of information more broadly (e.g. sacred sites, women's business, and men's business).

- Establishing mechanisms that incorporate the balance between collective and individual identity.
- Establishing a community advisory group and respecting community's decisions regarding the way research is to be conducted, right from project conception to conclusion.
- Considering the use of Aboriginal and Torres Islander standpoints and methodologies when developing research proposals, where appropriate.

Native American Center for Excellence

The Native American Center for Excellence (subsidiary of Substance Abuse and Mental Health Services Administration in the United States) *Steps for Conducting Research and Evaluation in Native Communities* document gives a high-level pathway for researchers wanting to partake in culturally safe research with Native Americans (Native American Center for Excellence, 2021).

The steps it details are outlined below:

1. *Establish relationships* – building rapport and credibility must happen well before the development of research protocols. Evaluators should attend Native meetings, ceremonies, and other social and cultural events to develop relationships so that they come to understand the Native community and are understood by it.
2. *Appreciate history and culture* – awareness of trauma experienced by tribe historically, as well as the personal histories of the individuals who are most likely to be involved in the study. It is also important to understand the historical relationship between the community and the evaluator's institution, which may be considered elitist.
3. *Demonstrate respect* – tangible respect for the community and its indigenous expertise must be shown. Sometimes this includes developing a Memorandum of Understanding (MOU) that includes a clear statement of Native norms and values that are to guide the collaboration.
4. *Proceed in community time* – evaluators must understand that deadlines and schedules may be substantially varied dependent on community priorities and that Native and Western time may well diverge.
5. *Embrace a strengths perspective* – must build on the community's strengths. The evaluator must be able to clearly specify how the study and its data would be of direct benefit to the community.
6. *Awareness of community readiness* – programme may need to undergo a careful and potentially time-consuming process of adaptation to ensure it integrates traditional practices and is congruent with tribal culture.
7. *Transparency* – evaluators must be candid about initial assumptions and expectations concerning the research, especially with how data will be captured and how results will be reported and interpreted (and by who).
8. *Respectful of research protocol* – evaluators should look to set up advisory boards to make sure what is being done is congruent with tribal expectations and customs.
9. *Privacy* – evaluations of Native programmes should be focused inward in the particular contexts that they are administered. Comparison across Native communities may not be appropriate as it could suggest one community is better than another.

10. *Employ blended research methods* – must be sensitive to the need to employ culturally-grounded qualitative methods in data collection protocols that include indigenous ‘ways of knowing’ as valuable approaches to scientific enquiry.
11. *Reality checks* – the community must be kept fully informed as the study progresses, and their efforts and contributions must be validated and recognised. Additionally, regular meetings/forums with the community allows for culturally appropriate interpretation of findings and therefore application to real-life settings.
12. *Intellectual and cultural property rights* – evaluators and researchers must be sensitive to community’s rights to control the dissemination of their tribe’s intellectual and cultural property, as well as recognition and credit for their scientific knowledge that results from the study. Key community members should also be engaged as co-authors who participate in the writing of reports and publications and should have primary roles in structuring and developing the narrative. In some cases, it may be appropriate for the evaluator/researcher to entirely avoid dissemination of research findings.
13. *Plan for sustainability* – if possible, evaluators/researchers should work alongside communities to try and institutionalise the relationships and funding that help to support sustainable health developments. Part of this involves collecting and presenting study data in a way that will support the community’s efforts to secure continued programme support.

Canadian Panel on Research Ethics – Research Involving the First Nations, Inuit, and Métis Peoples of Canada

Within the Canadian *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)* document there is a chapter dedicated to research involving the First Nations, Inuit, and Métis Peoples of Canada (Government of Canada, 2019).

The purpose of the chapter is to illustrate:

- Firstly, the significance and unique status of the Indigenous Peoples of Canada in the Constitution Act 1982.
- How the values of respect for human dignity and core principles of Respect for Persons, Concern for Welfare, and Justice (from the first chapter) are applied in Indigenous research.
- The respect necessary for Indigenous knowledge systems by ensuring that the worldviews of First Nations, Inuit, and Métis peoples are represented in planning and decision-making right throughout the research process.
- The respect necessary for community customs and codes of research practice to ensure balance in the relationship between researchers and participants, and mutual benefit in the researcher-community relations.
- Overall, culturally appropriate, and ethical ways for researchers to engage with Indigenous communities to serve their wants and needs to improve their health and wellbeing outcomes.

There are some data governance frameworks internationally that outline requirements

Data governance and control surrounding use, capture, and storage is necessary in maintaining or building an effective clinical trials system. The data governance frameworks showcased below provide researchers and research groups with context, direction, and examples of how to approach data governance correctly.

NLM Data Governance Framework feeds into open access, shareability, and usability of data

The purpose of the National Library of Medicine (NLM) Data Governance Framework is to harmonise specific common data models (CDMs) to ensure data can be easily accessed, transferred, interpreted, and used in a wider range of 'real world' health research settings (i.e. large population analysis).

Effectively, the framework document is designed to:

- Describe the foundations of data governance for clinical research.
- Recommend a governance structure to establish and maintain policies and procedures for safe and effective data capture and use.
- List some documents that ICs should consider when creating/adopting their own governance and system access requirements.
- Share best practice where possible (National Library of Medicine, 2020).

It takes learnings and information from different sources, including PCORnet, Informatics for Integrating Biology and the Bedside (i2b2 ACT), and Observational Health Data Sciences and Informatics (OHDSI).

The guidance covers (not exhaustively):

- Data security and the corresponding institutional policies.
- Controlling system access and involvement in trials.
- Data integrity and control over who can change/access the data.
- Data quality, including accuracy, completeness, and fitness for purpose.
- Board responsibilities in maintaining oversight.
- Board membership and conduct.
- Data use and sharing agreements.
- Publication, intellectual property, copyright etc.

Australian Institute of Health and Welfare (AIHW) Data Governance Framework

The Australian Institute of Health and Welfare (AIHW) is an independent statutory Government department that serves to provide accessible information and statistics about the health and welfare of Australian people to support better policy decision making and service provisions. The current version of the document is for internal use, but an adaptation is being developed for external stakeholders (AIHW, 2021).

Although not exclusively for clinical research data, the Institute has recently published a Data Governance Framework that outlines the requirements of any health data that is intended for use by AIHW. Ultimately, a framework like this may provide a solid reference point for data governance standards in clinical trials settings.

The document is relatively comprehensive and provides information about:

- Data governance concepts, the nature of data, integration and linkage, secure access, metadata standards, and other policies and procedures plus tools to use.
- The legal and regulatory environment and the interaction that has with data and governance, including privacy and freedom of information.
- Structures and explicit roles in data governance, including for boards, ethics committees, and other staff.
- Systems and tools to support data governance, such as the AIHW ICT framework and data catalogue.
- AIHW data policies, guidelines, and procedures regarding data lifecycles, use, and storage.

There are bodies that help with actioning the guidance in the above data governance frameworks

An effective learning healthcare system relies on the ability to translate and store information in a standardised, easy to read and manipulate format. Some of the key benefits of having standardised information are:

- clear, logical frameworks that allow for easy data navigation and use
- the ability to compile information across sources, creating extensive longitudinal databases
- efficiency gains in data use and data sharing
- increases in the ability to re-use data for new trials and translate data effectively for clinical care.

Data governance frameworks and guidance are not strong enough on their own to ensure researchers and research groups follow best practice when considering the use, capture, and storage of data. The examples below show specific international best practices that promote common data models and help to action the guidance from the above frameworks.

The NIH Collaboratory Distributed Research Network (DRN) enables easy, safe data access in the US

The NIH Collaboratory Distributed Research Network (DRN) has the purpose of enabling collaboration between NIH funded trial investigators and other not-for-profit sponsors based in health plans that participate in the US Food and Drug Administration's (FDA) Sentinel System. The DRN was created by the Electronic Health Records core working group at the NIH Collaboratory, with the objectives of enabling distributed remote analysis of research datasets across health systems and acting as a central node for the tools and infrastructure to utilise electronic health records in clinical research (NIH Collaboratory, n.d.-a).

The DRN fully leverages the data from the Sentinel System, as well as its methods, tools, and querying infrastructure. One key feature of the DRN is it can directly contact providers and health plan members to collect new information, or in support of randomised clinical trials, especially across multiple sites (NIH Collaboratory, n.d.-d). The Electronic Health Records core working group's model aims to:

- Develop and test phenotype algorithms (i.e. algorithms to determine presence of disease) within and across projects (NIH Collaboratory, n.d.-c).
- Identify data validation best practices with respect to statistical approaches, data capture methods, electronic health record use, and quality assessment.
- Use accredited standards-developing organisations to move these measures into practice.

Alongside this is the Ethics and Regulatory core working group with the objectives of ensuring that the easily accessible data is still private and honours potentially vulnerable subjects and information (NIH Collaboratory, n.d.-b).

Developed systems are used in Demonstration Trials at the forefront of medical research, with the intention of having results, methods, data systems, and models shared widely across jurisdictions and fields to encourage uptake of uniform data systems and easy, open, and transparent access to health data as well as to foster partnerships. The systems are being used for:

- clinical trials feasibility
- hypothesis testing
- development of inclusion/exclusion criteria
- conducting multi-centre trials.

PCORI's PCORnet has a common data model much like NIH Collaboratory

The Patient-Centred Outcome Research Institute (PCORI) is a US based clinical trials establishment with the intent of funding research driven by patients, caregivers, and the broader healthcare communities wants and needs in terms of health outcomes (PCORI, n.d.-a).

PCORI operate the National Patient-Centred Clinical Research Network (PCORnet), operating like NIH Collaboratory's DRN in the sense that they have a Common Data Model that standardises data responses from different data sources and health providers to allow for easy, fast analysis of data (PCORI, n.d.-b).

The Model takes data points from all types of clinical information systems and standardises them in their descriptiveness and their location, meaning users of PCORnet can ask the same questions to millions of patients simultaneously across multiple (sometimes very different) systems. The benefit of this is the widespread capture of data across multiple systems in a uniform format that allows for consolidated, easy, fast analysis of data.

The NIHR Health Informatics Collaborative (HIC) similarly streamlines data records and access

The UK NIHR Health Informatics Collaborative (HIC) is also an example of targeted efforts to standardise data across multiple clinical research facilities and other healthcare providers. HIC is a collaboration between the NHS trusts tasked with improving the quality and availability of patient information to allow for translational research (Health Informatics Collaborative, n.d.).

It is a metadata catalogue with the specific objectives of:

- Maintaining catalogue standards for each of the NHS trusts to ensure data is properly recorded.
- Ensuring data is comparable, and where possible mitigating or eliminating differences in recording standards.
- Ensuring records have the required detail of information for high quality care, service evaluation, and translational research.
- Facilitating the sharing of data between trusts and partner organisations through a governance framework.
- Upholding publication policies to ensure contributors receive appropriate credit.
- Streamlining the process for data re-use for scientific progress and patient benefit.

The English Clinical Practice Research Datalink (CPRD) consolidates data from different primary care providers

Another example from England is the Clinical Practice Research Datalink (CPRD). It is an initiative jointly sponsored by NIHR and the Medicines and Healthcare Products Regulatory Agency and collects anonymised patient data from a network of GP practices across the United Kingdom (CPRD, n.d.).

The primary care data that they collect is then linked to a range of other health related data to provide a longitudinal UK population health dataset of over 60 million patients, including 16 million currently registered.

Data policies across best practice are similar in encouraging uniform data and open access sharing

Uniform data and standardisation of reporting across different entities and activities makes combining datasets much easier and therefore widens the potential for the data to be used in an array of meaningful ways. Multiple bodies around the world have open access policies in the hope of ensuring any data generated or used in studies they have funded becomes open access and free for use with other researchers. This is particularly important for data that is unique and not easily replicated.

A 2019 report showed that Aotearoa is at a significant disadvantage when it comes to open access publishing of research findings and data in universities (Universities NZ, 2019). Elsewhere in the world (and particularly in the EU and US) research funders, governments, and universities have coordinated efforts to make sure research is widely available and re-usable for no cost to the researcher. Although this paper is specific to university research, the main messages are applicable to wider research nationally.

Some important findings from the paper are:

- Research articles in open repositories which can be accessed by anyone are cited 66 per cent more than those behind paywalls.
- 51 per cent of university research which is publicly funded by our biggest research funders (HRC, Marsden, etc.) is behind a paywall, meaning it is inaccessible to government agencies and the public.

- 41 per cent of research articles are openly accessible where any of the authors are from a university in Aotearoa.
- Open articles were referenced in the media 3.5 times more than closed ones and mentioned in policy documents twice as often in Aotearoa.

It is hard for any funding body to enforce data sharing (especially to one location) in a health research context because of the variety of potential data types and settings the data may captured in. These conditions can lead to complex, nuanced datasets that have high risk of being misused, are not appropriate for public sharing, or are simply not compatible. Therefore, most guidance and policies documented in this section serve to strongly *recommend* the sharing and open access of data and provide mechanisms to ensure the barriers to sharing are as low as possible.

Support is often given through walkthroughs and guidance of data sharing policies, as well as references and recommendations surrounding appropriate data repositories to use given specific interest/research areas.

NIHR Open Research + Journals Library

NIHR Open Research is a platform for all NIHR-funded researchers to publish any results they think are worth sharing (important note about researcher discretion in determining what is worth sharing). Through doing so, researchers’ findings are published, peer-reviewed transparently, and receive editorial guidance speedily to ensure knowledge is translated efficiently.

The process goes as follows:

Figure 15: NIHR Open Research publishing process for articles and data



Source: adapted from (NIHR Open Research, n.d.-a)

A similar process exists for standalone documents. Once submitted and checked in-house, documents are published on the repository and given a digital object identifier (DOI) and become citable.

Importantly, there is relatively comprehensive guidance for how reports should be prepared (i.e. the appropriate format) and how data should be stored, coded, and documented, adhering to the FAIR principles (**F**indable, **A**ccessible, **I**nteroperable, **R**eusable) (NIHR Open Research, n.d.-b; Wilkinson et al., 2016). NIHR Open Research does not have its own data repository, instead suggesting researchers upload their datasets to any on a list of approved repositories.

NHMRC Open Access Policy in Australia for health data sharing

The NHMRC Open Access Policy is reflective of the wider Australian Government's commitment to open access, open data, and intellectual property management. Effectively, the policy aims to ensure open access sharing of publications from NHRMC-funded research and encourage innovative open access to research data for other use by other researchers (NHMRC, 2019). The main motivations for this are:

- To increase reuse of data (i.e. increase the value of data that is held).
- To improve research integrity and quality of findings.
- To generate a stronger knowledge economy.

NHMRC do not host their own repository for publications of NHMRC-funded research, however, require that any peer-reviewed publication must be made openly accessible in an institutional repository or other acceptable location (publisher website, subject repositories, etc.) within a 12-month period from the date of publication. Additionally, all metadata from the study must be made openly available within a 3-month period from the date of publication.

The Policy document also links to the NHMRC Australian Code for the Responsible Conduct of Research, and the subsequent document detailing the appropriate management of data and information in research which holds more information about how to display, store, and use data. It also references the FAIR principles like the NIHR Open Research Policy (NHMRC, 2019).

NIH guidance for data is like NIHR and NHMRC

The NIH Data Sharing Policy and Implementation Guidance produced by the NIH Grants & Funding serves to outline how researchers should prepare, use, and store data in NIH-funded research to ensure open access for future research and translation purposes. The guidance broadly covers:

- The applicability of the guidance (i.e. who must follow it and in what situation).
- The necessary actions in implantation of the data-sharing policy including timeliness of sharing, privacy issues, methods of sharing, and documentation.
- What to include in an NIH application and the necessary components for success.
- Examples of data-sharing plans for researchers to follow (National Institutes of Health, n.d.-a).

In terms of where the data should be shared, the NIH does not endorse or require sharing in any specific repository, simply encouraging researchers to select that which is most appropriate for their data type and discipline. The Trans-NIH BioMedical Informatics Coordinating Centre (BMIC) published a list of NIH-supported (i.e. recommended) data repositories that researchers can use as a reference for where to share their data (National Library of Medicine, 2022).