



**Australian
Clinical
Trials
Alliance**

International Best Practice Towards a Learning Healthcare System

A scoping activity to map international approaches to embed clinical trials into the healthcare system

AUGUST 2018 (last updated May 2022)

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A Learning Healthcare System (LHS) is defined as a system in which...

“science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”

Institute of Medicine (US)

KEY POINTS

- A move to an LHS requires buy-in from all stakeholders, including health system leaders and health professionals who are not research active.
- Traditional ethics and governance frameworks apply poorly to pragmatic trials. Continuous improvement and research form a continuum that should be better valued as a core responsibility of delivering safe and effective healthcare.
- All stakeholders should value clinical trials as part of an LHS and be able to convey their importance with patients and the public.
- Wider access to research design and trial coordination services is necessary to support an LHS and to avoid the potential for missed opportunities or wasteful research practice.
- More resources and training are needed to develop and conduct trials with novel designs suitable for an LHS.
- The lack of interoperable digital infrastructure makes it difficult to conduct rapid-pace trials of sufficient size to support decisions in an LHS.
- The lack of clarity around privacy and the use of health data impedes the move to an LHS.
- Changing the culture of the health service is seen as one of the biggest challenges.

EXECUTIVE SUMMARY

Many treatments and treatment strategies enter routine clinical practice with neither evidence of effectiveness nor of cost-effectiveness. This vacuum of evidence contributes to variation in care and unsustainable growth in healthcare expenditure. There is also widespread evidence that many treatments that have been proven to be effective and cost-effective are not implemented in clinical practice.

A Learning Healthcare System (LHS) is gaining traction as a way to achieve the best possible patient outcomes at reasonable cost. An LHS is characterised by the continuous generation and implementation of knowledge from clinical research 'embedded' within healthcare delivery. Internationally, concerted efforts are being made to move towards an LHS. There is a broad consensus on the factors that are critical to success.

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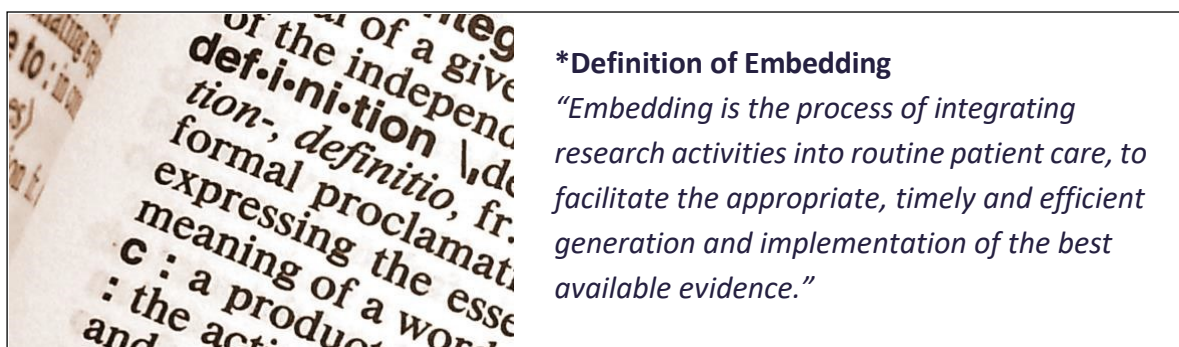
INTRODUCTION

The clinical research enterprise is not producing the evidence decision makers arguably need in a timely and cost-effective manner; research currently involves the use of labor-intensive parallel systems that are separate from clinical care¹

The ideal Learning Healthcare System is characterised by the continuous generation of knowledge integrated with the provision of care. Over the past decade, many countries have embraced the notion of a Learning Healthcare System in which decisions about health and health care are supported by continuously updated, high-quality evidence.

The Australian Clinical Trials Alliance, on behalf of the Clinical Trials Networks (CTNs), wished to identify international best practice relating to the ‘embedding’ of clinical research into the healthcare system, to inform initiatives that maximise the ability of CTNs to conduct efficient and timely ‘public good’ research. The value of ‘public good’ research conducted by CTNs has been clearly demonstrated by a report conducted by the Commission on Safety and Quality in Healthcare in which the economic benefits from application of trial results was \$5.83 per year for a one-off investment of \$1 in conducting the trials and maintaining the network².

The creation of a Learning Healthcare System encompasses many domains of work; however, this report focuses primarily on activities that support the conduct of clinical trials. It features three countries; the United States (US), Canada and the UK, as these countries are making concerted efforts to embed* clinical research within their healthcare systems.



Examples of National entities that coordinate embedding activities

United States (US): In the US, the move towards a Learning Healthcare System has a large number of effective champions, with the Institute of Medicine (the National Academies of Medicine) beginning work in 2006 through a series of [Roundtables](#).



“By the year 2020, ninety percent of clinical decisions will be supported by accurate, timely, and up-to-date clinical information, and will reflect the best available evidence.”

Charter IOM Roundtable on Value & Science-Driven Health Care

To strengthen the national capacity to embed cost-effective, large-scale trials into the health system³, the National Institutes of Health (NIH) created the Health Care Systems Research Collaboratory ([NIH Collaboratory](#)) to support the design, execution and dissemination of a series of demonstration projects using pragmatic research designs. The Patient-Centered Outcomes Research Institute ([PCORI](#)) is a non-governmental institute charged with evaluating and conducting comparative effectiveness and other health services research. In an effort to build infrastructure, PCORI has invested more than \$100 million USD in the development of a national ‘network of networks’ known as the National Patient-Centered interoperable Research Network (PCORnet) that is supporting the conduct of much larger trials that can be embedded into the health system.

Federal agencies such as the Agency for Healthcare Research and Quality ([AHRQ](#)) are funding studies to evaluate and demonstrate effectiveness in Learning Healthcare System models. The AHRQ disseminates findings published by PCORI and other government-funded entities that sponsor comparative effectiveness research.

Canada: The Canadian government’s [Strategy for Patient-Oriented Research](#) (SPOR) is a coalition tasked with the integration of research into care. The strategy is supported by the Canadian Institutes of Health Research (CIHR) which provides a \$1 billion annual investment to fund SPOR-related research. SUPPORT Networks and SUPPORT Units are two key elements of the Canadian strategy. SUPPORT Networks are national collaborative research networks involving researchers, patients, policy makers, academic health centres, health charities and SUPPORT Units, provide the necessary expertise to enable patient-centred research. The [Canadian Clinical Trials Coordinating Centre](#) has been created to strengthen the clinical trials environment by supporting initiatives such as expediting trial set-up and collecting clinical trial metrics.

England: In 2006, a review of health research funding⁴ and new policy⁵; placed a strong focus on research that ‘meets the needs of patients and the public’. The creation of the National Institute of Health Research ([NIHR](#)); a single patient-centered agency focused on applied science, has greatly increased patient access to clinical trials across England. Since 2006, it has provided £1 billion of annual funding and 53% of this investment is allocated to building and maintaining infrastructure with 25% of that, funding and supporting a trained workforce of about 10,000 research nurses and other staff embedded across the NHS. The [Health Technology Assessment Programme](#) is the largest of the NIHR programs.



Clinical research has moved from an activity previously carried out by a few large teaching hospitals, to high levels of participation – ‘In 2017, 99% of NHS Trusts and 48% of General Medical Practices were actively engaged in clinical research.’

NIHR

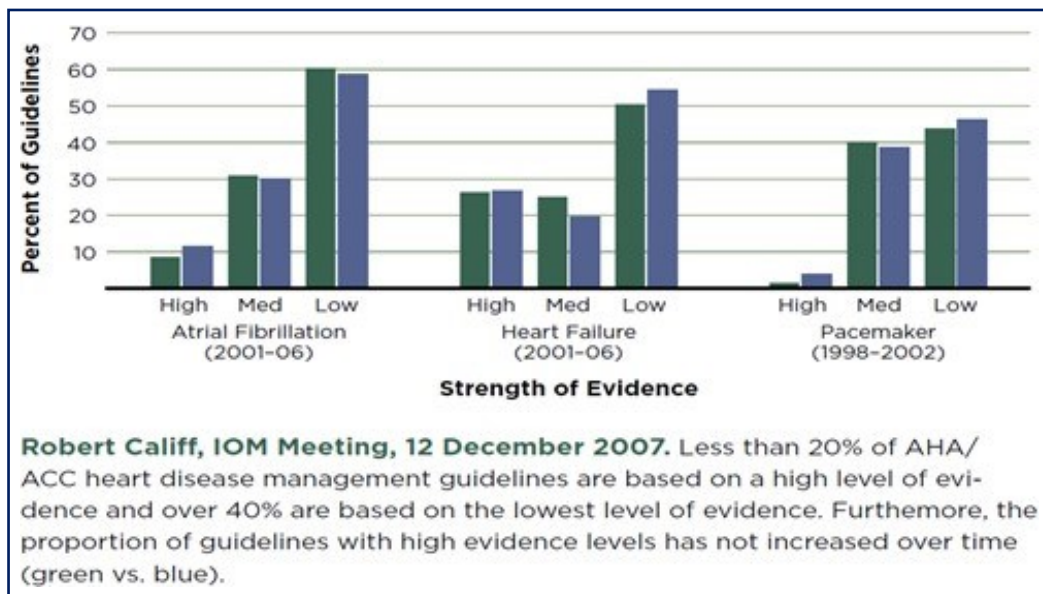
BENEFITS OF A LEARNING HEALTHCARE SYSTEM

A learning healthcare system continuously and reliably captures, analyses, and delivers the best available evidence to guide, support, tailor, and improve clinical decision making and care safety and quality ⁶

The Learning Healthcare System is a conceptual framework that has attracted international interest for its potential to address the challenges faced by the current health-care system. It is being driven by a growing appreciation that health systems need better evidence. Within such a system, electronic data from multiple sources is repurposed for research to dramatically accelerate the creation and validation of the knowledge required to improve clinical care and translation of that knowledge into practice.

Clinicians depend on reliable evidence to care for their patients. However, many of the decisions made as part of routine care are not supported by high-quality evidence, resulting in sub-optimal, sometimes dangerous practice and a significant waste of healthcare resource. Better evidence is a necessary pre-requisite, though often not sufficient, to achieve appropriate disinvestment. Systems that categorise levels of evidence rank randomised controlled trials (RCTs) and systematic review of RCTs as the highest level of evidence and case series or expert opinions, the lowest^{7,8}. However, traditional RCTs are expensive and even when they yield definitive results, they are sometimes not fully generalisable to the populations that they intend to treat and often take years to be translated into practice⁹. As a result, surprisingly little of clinical practice is based on high quality evidence. This is starkly illustrated by examination of the strength of evidence found in clinical practice guidelines by one group in the US.

FIGURE 1: Inadequate evidence to guide care



The successful transition to a Learning Healthcare System will depend on health system leaders creating an environment of continuous learning that filters down to clinicians and patients, who in turn, must believe there is significant value in this new approach. Comparative effectiveness trials are a foundational element of such a system; however, to conduct trials that will rapidly and cheaply generate evidence for the health system, several core elements must be in place.

ELEMENTS TO SUPPORT THE EMBEDDING OF CLINICAL TRIALS

FIGURE 2: Six requirements for embedding clinical trials



1 PROPORTIONATE REGULATION AND GOVERNANCE

*The disproportionate effort expended in the regulation and management of research comparing standard treatments remains the most formidable disincentive to health professionals, patients, and researchers who wish to collaborate to confront uncertainties about the effects of health-care interventions in everyday practice*¹⁰

1.1 ACTIVITIES TO STREAMLINE ALL CLINICAL RESEARCH

Ethics and governance approval are recognised in all countries as becoming increasingly burdensome and disproportionate to the risks posed to participants, particularly for pragmatic trials that apply variants of standard care and represent no incremental risks when compared to care outside a trial. Most research ethics codes presume that the only interventions that will be tested in a clinical trial are experimental with little or no prior evidence of safety and effectiveness. As a consequence, most codes apply poorly to the evaluation of interventions that are already part of the spectrum of standard care. More proportionate systems are needed for evaluating alternative interventions that are part of standard care, are known or believed to be safe and effective, but for which it is not known if there is an option that is best.

In the US and Canada, the universal use of single ethical review systems has only recently been implemented and duplicative ethics review is still a major impediment. However, the move towards the proportionate approval of research is evident, with a wider range of research (compared to Australia) that is either exempt from ethics review or eligible for a low risk, expedited review pathway.

In England, where single ethics review has been in place for many years, institutional governance approval was widely recognised as the '*single greatest barrier to health research*'¹¹. The Health Research Authority (HRA) has been formed to address this and other impediments and is streamlining the research process. In parallel with this work, the NIHR has introduced national metrics to drive process improvement which has resulted in a 75% reduction in governance approval times. Metrics focused on research delivery have also been implemented and each site's performance is [openly published](#). In 2017, 83% of publicly funded research was delivered on time and to target recruitment and only 9% of active sites were non-enrollers. Streamlining initiatives include:

- *HRA Approval* – Implemented in 2016, HRA approval in England centralises and combines ethics and governance approvals to provide a single approval using the UK's national application platform¹². Each participating site in a multicentre trial 'accepts reliable assurances' that all governance and legal compliance checks have been completed and undertakes a swift local assessment of capacity and capability before agreeing to participate. This has contributed to reducing the median time from trial application to first patient recruitment from 231 days (Q3 2015/16) to 142 days (Q3 2016/17)¹³.
- *The Research Passport Scheme (NIHR)* – To address the issue of researchers working across multiple sites needing repeated and inconsistent 'pre-engagement checks' (e.g.

police / occupational health) in order to access each research sites, the [Research Passport](#) expedites study set-up by providing a mechanism to obtain one set of checks that are accepted by all sites. While implementation of such a scheme may have challenges, if implemented successfully major efficiencies would be achieved.

- [Attributing the costs of health and social care Research & Development \(ACORD\)](#): The challenges around the definition and allocation of research costs and indirect costs was a major disincentive for organisations to engage in research and researchers faced problems when determining costs for investigator-led studies. [AcoRD](#) provides a clear framework for their expedited allocation of Research Costs, NHS treatment costs and NHS support costs.

1.2 ACTIVITIES TO STREAMLINE COMPARATIVE EFFECTIVENESS TRIALS

The routine implementation of comparative effectiveness trials is a key element in realising the vision of the Learning Health System but there is widespread recognition that achieving this at scale, will require adjustments to regulatory/ethics frameworks^{14,15,16}. The US, in particular, has recognised that regulatory frameworks designed for conventional trials apply poorly to minimal risk comparative effectiveness research, especially in areas such as informed consent. The NIH have a proactive program of work aimed at creating a regulatory and governance environment that facilitates the closer coupling of service delivery and research through the conduct of pragmatic trials. The [NIH Collaboratory Ethics and Regulatory Core](#) has been tasked with addressing common areas of concern. The US has amended regulation and policy to facilitate comparative effectiveness trials including facilitating and encouraging the use of altered or waived consent models for minimal risk trials^{17,18}. There is also evidence of the wider use of consent processes such as ‘front of door consent’, for use of data and tissue in research, and ‘consent to contact’¹⁹, to enable patients to be approached for clinical trials by individuals other than their direct care team. Fragmented legal frameworks and inconsistency in the interpretation of privacy laws is seen as a significant impediment to the move to a Learning Healthcare System in all countries. To facilitate the secondary use of data for research, the UK government has introduced a national data opt-out model²⁰ to increase access to deidentified data sets.

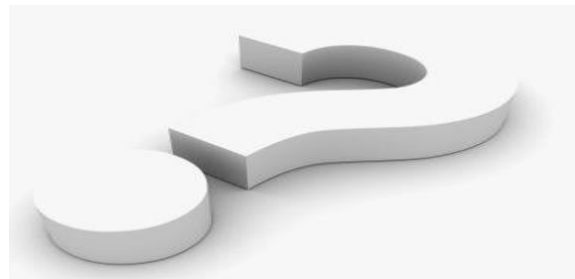
2 PUBLIC AWARENESS AND ACCEPTANCE OF RESEARCH

The lack of awareness and understanding of research amongst the general public has been recognised as an important barrier to embedding research. Work is underway in all countries to address the knowledge and information gap.

Most patients assume that only treatments that are proven to be effective would be in routine use. Healthcare systems and clinicians have had little incentive to inform the public about how little of medicine is based on high quality evidence. Consequently, the concept of comparative effectiveness research is poorly understood by the patients and the public. There can also be a misperception that clinical trials would only be offered when there are no other treatment options left. While clinical trials do offer important access to novel treatments for patients who have exhausted all other options, misunderstanding between the roles of experimental and comparative effectiveness trials creates confusion and can inhibit recruitment into and acceptability of trials of variants of standard care.

In many countries, there is increasing recognition that consumers are integral stakeholders in the development of evidence to inform healthcare. This, coupled with the growing awareness that the LHS provides a tangible means to addressing the lack of evidence, is driving collaborations between patient communities, regulators and researchers to improve the clinical trial enterprise. To support the move to an LHS, awareness campaigns are being engineered to allow patients to better understand the need for higher quality evidence and to motivate the demand for more trials to generate that evidence.

In England, the current strategic plan, [‘Best Research for Best Health: The Next Chapter’](#) set out a new program to encourage public engagement and participation in health research. The plan brought together several initiatives. The [NIHR OK to Ask Campaign](#) more patients and carers to ask about the research opportunities so that it becomes a natural part of conversations at hospital or GP appointments. To strengthen the NHS's commitment to health research, the NHS Constitution for England (The Patient's Charter), now pledges to inform patients of research studies in which they may be able to participate. Exploration of how best to support consumers to raise awareness of research, has culminated in the Patient Research Ambassador Initiative which focuses on promoting health research from the patient's point of view. [‘I am Research campaign’](#) has focused on promoting the benefits of clinical research. The UK government requires the NIHR to monitor the impact of their awareness activities through an annual survey of public attitudes to clinical research.



The Knowledge and Access Gap

In 2013, the NIHR conducted a mystery shopper exercise in NHS hospitals. Of the 80 hospital sites visited, the majority failed to provide information on clinical research activity in their reception area, on notice boards, on electronic screens or leaflet displays. Nearly half of the receptionists approached told the mystery shopper that clinical research was not something their hospital got involved in.

In the US, the NIH are conducting a national communication campaign and survey to increase public awareness and interest in clinical trials. The survey²¹ assessed the impact of multiple message which described the value of clinical trials, normalised trial participation and proposed acceptable calls to action to talk with doctors and visit websites for more information. The Institute of Medicine is focusing on improving public understanding of the nature of evidence, the dynamic character of evidence development, and the importance of insisting on medical care that reflects the best evidence²².

Public awareness activities are often coupled with ‘matching’ or ‘self-referring’ services. Examples include the NIH Clinical Centre alliance with [ResearchMatch](#), US Alzheimer’s Association [TrialMatch](#) and the NIHR [Join Dementia Research](#) initiative.

3 ENABLING INFRASTRUCTURE

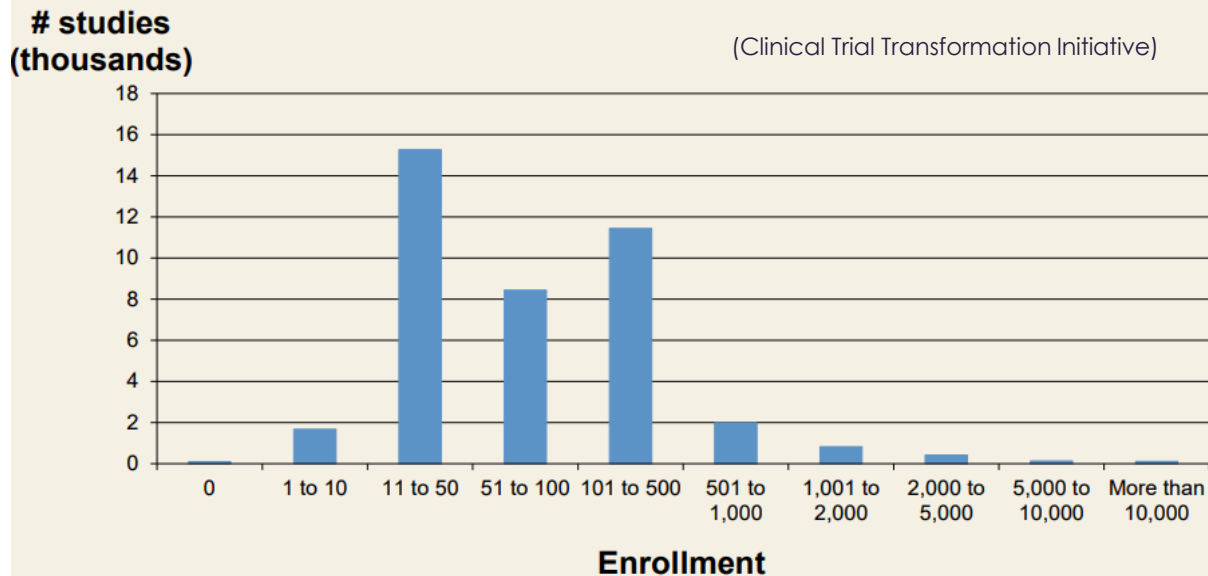
3.1 INFRASTRUCTURE TO SUPPORT TRIAL CONDUCT

Randomised trials are often considered to be the gold standard for clinical development. However, a report from the US Tufts Centre illustrates the increasing complexity and work burden associated with many modern RCTs²³.

There is no deficit in ‘good ideas’ for trials or of knowledge about how to design a trial that, if conducted, would be valid but there is an important lack of capacity to conduct and execute trials that meet the requirements of end-users including patients, clinicians, and policymakers. It is the availability of infrastructure, both human and physical, that determines whether trials can be conducted that are fit for the purpose of generating evidence to improve patient outcomes.

In the US, the [Clinical Trial Transformation Initiative \(CTTI\)](#) a public-private partnership comprising more than 60 organisations, has developed resources to reduce the burden of trial conduct and improve trial efficiency. CTTI has identified three key features of trials that determine the risk-benefit balance of therapies. Firstly, they must be large to identify moderate treatment effects, secondly, they must be simple, to reduce both work burden and trial costs and thirdly, they must be randomised to limit bias and confounding effects. An analysis of trials registered in [ClinicalTrials.gov](#) shows the disparity between the trials that are recommended and the trials that are conducted²⁴.

Number of Subjects/Study (Anticipated or Actual enrollment)



Cliff RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A.
Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307(17):1838–1847

STATE OF CLINICAL TRIALS

An analysis of 96 346 clinical studies concluded that the clinical trials registered in ClinicalTrials.gov are dominated by small, single centre trials (the median number of participants was 58 for completed trials) with significant heterogeneity in methodological approaches:

'The fact that 50% of interventional studies registered from October 2007 to September 2010 include fewer than 70 participants by design may have important policy implications.'

Trial Networks

Trials that are designed to provide definitive evidence regarding the value of a health intervention cannot be conducted at a single site. There is no single site, regardless of size or reputation, that can offer sufficient expertise, facilities and capacity to conduct trials that are valid and have adequate generalisability. In many countries this has encouraged collaborative groups of clinicians – doctors, nurses, and other health professionals to come together with experts in trial management and analysis to form clinical trial networks. These networks provide access to many more sites (creating critical mass for sample size and generalisability), provide pathways for sharing of resources and expertise, and create a community that identifies and solves clinical problems that are important for patients.



Trials Acceleration Programme (TAP)

Blood cancer trials are notoriously difficult to set up and can be slow to deliver results. TAP has given haematological oncology patients accelerated and wider access to early phase trials. Working within the existing NIHR Cancer Research Network, TAP's centralised management minimises the 'red tape' to establish trials and deliver accelerated results via disseminated patient recruitment across network centres. The 'network' is offered to companies with promising new drugs. Early results show a 50% reduction in set-up time and significant reduction in costs per patient. TAP has ratified trials that would not otherwise have taken place in the UK.

Coordinating Centres for Trial Management

Determining the most appropriate trial design is not always easy and when trial design and methods are poorly chosen, trial management and delivery problems ensue. In the UK, the increase in clinical trials activity has been underpinned by an increase in clinical trial management expertise. Registered clinical trial units (CTUs) are specialist units which have been set up with a specific remit to design, conduct, analyse and publish clinical trials. They bring together a range of trial expertise within one centre, working in a collaborative relationship with Principal Investigators to deliver high quality and efficient clinical trials. CTU have access to support funding from the NIHR and their use for investigator-led trials is widely encouraged. The involvement of a CTU is considered a quality mark to funders. It also enables universities and public health organisations to confidently take on the role of trial sponsor, as the delegation of the majority of sponsor responsibilities to an accredited CTU mitigates the risks of sponsorship.

Across the US, many research active centres provide centralised clinical trial support and infrastructure. For example, the Mayo Clinic and Harvard Catalyst bring together the core resources and clinical expertise required to conduct high quality trials.

Developing infrastructure to improve the quality of trial design and management has been central to the Canadian strategy with the SPOR SUPPORT Units specialised and multidisciplinary methodological expertise, including research design, biostatistical analyses and data management. These units also support the development of the next generation of methodologists.

3.2 DIGITAL INFRASTRUCTURE

The rapid advancement and availability of electronic health records (EHR) is transforming the way clinical research can be conducted and has the potential to substantially enhance the efficiency of the conduct of trials (i.e. the dollars necessary to answer a clinical question definitively). Increased access to EHRs, and other real-world health data sources, has made it possible to design trials that can be embedded into the health system by providing ways to: identify and monitor specified populations, support patient recruitment, detect early safety

signals and capture trial outcomes. EHRs can also significantly lower the cost of trials by integrating point-of-care randomisation and data capture into clinical processes. The US government has provided a \$30 billion federal investment to promote the 'meaningful use' of health information technology as a central part of their plan to transform healthcare delivery. In the UK, research with EHR data has been recognised as a key activity in the Department of Health's national health research strategy.

The [NIH Collaboratory's Living Textbook](#) includes a comprehensive analysis of some of the issues relating to the use of EHR in pragmatic trials. Their Demonstration trials are conducted through the '[Distributed Research Network \(DRN\)](#)' that enables investigators to collaborate in the use of electronic health data, while also safeguarding protected health information and proprietary data. The Collaboratory's Phenotype, Data Standards, and Data Quality (PSQ) 'Core' working group is developing capabilities for evaluating, using, and sharing electronic health data that address variations in data collection and representation across different organisations in a research network²⁵. The model ensures that data are securely held by each partner organisation but are accessible through a querying mechanism, mitigating many of the privacy issues. The system is being used for clinical trial feasibility, hypothesis testing, development of inclusion/exclusion criteria and also can be used to conduct multicentre pragmatic trials.

Similarly, [PCOR.net](#) (an initiative of PCORI) is using its network of networks to conduct large scale comparative effectiveness trials. Data from health systems participating in PCOR.net are transformed into a common data model that enables the creation of analysis-ready standardised data to support both observational studies and clinical trials. By building the infrastructure to conduct them, [PCOR.net](#) is significantly reducing the amount of time and effort required to start studies.

In England, the NIHR [Health Informatics Collaborative](#) brings together five leading Biomedical Research Centres to conduct large university-hospital projects using a [metadata catalogue](#) to improve the quality and the availability of clinical data, and the way that information about this data is presented to healthcare professionals and researchers.

The US Department of Veterans Affairs (VA) have conducted trials that exemplify the direct translation of study results into clinical practice that defines a Learning Healthcare System. [One point of care trial](#) using 'adaptive randomisation' through their EMR system illustrates how research has been embedded into the VA's health service.

National Safe Havens: In England, the [Clinical Practice Research Datalink \(CPRD\)](#) holds national primary care data that is linked with other national data sets. Although primarily used for observational research (including confirmation of the safety of the MMR vaccine), it enables randomisation at point of care for primary care clinical trials through software integrated with Primary Care Electronic Health Record. This functionality has been used to conduct a real-world diabetes and RCTs on myocardial infarction and COPD patients¹³.

Registries: Some pragmatic trials have successfully used registries as a platform. The Aspiration during ST segment Elevation myocardial infarction (TASTE) trial²⁶, was the first registry-based randomised controlled trial where registries were used as online platforms for randomisation, case record forms, data collection and follow-up, enhancing administrative feasibility at greatly reduced cost (USD \$50 per patient approximately). The US Clinical Trials Transformation Initiative has also produced [guidance](#) on embedding clinical trials into registries.

4 PRAGMATIC DESIGNS THAT CAN BE EMBEDDED

The gaps in evidence-based knowledge suggest that systematic flaws exist in the production of scientific evidence. Although RCTs are our primary tool for evaluating healthcare interventions, many countries recognise that major change in how we conceive, design, conduct, and analyse trials is necessary. Much of this work is focused on identifying and addressing the challenges associated with conducting trials with pragmatic designs that can be embedded into the health system. This work centres around the removal of parallel systems for data management and the application of proportionate ethics and governance processes described earlier and also the development of appropriate trial designs that minimise disruption to clinical workflow.

FIGURE 3: Reasons to conduct pragmatic trials?

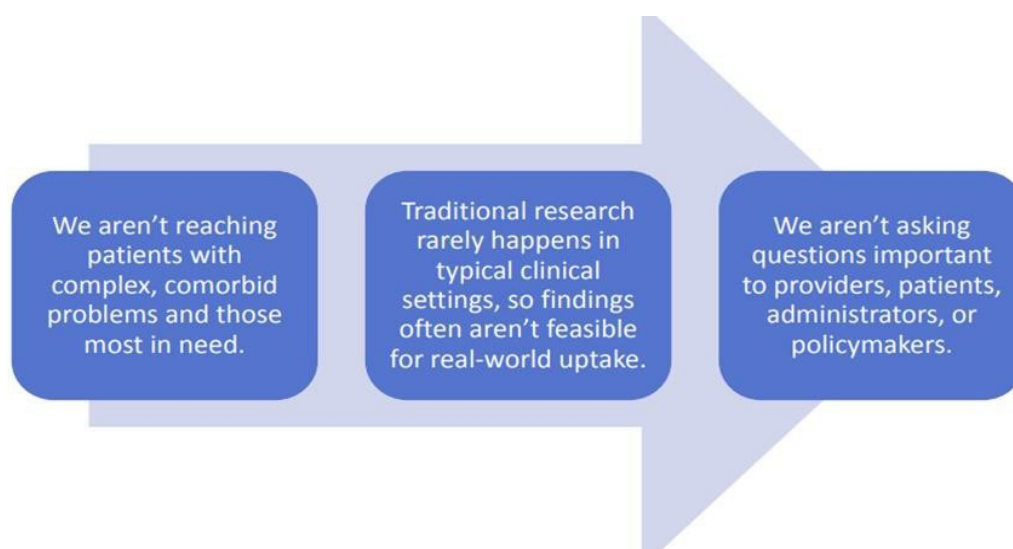


Image from the NIH Collaboratory
Introduction to Pragmatic Clinical Trials

4.1 PRAGMATIC TRIAL DESIGN

Pragmatic clinical trials (PCTs) can be defined as trials that are designed to test the effectiveness of the intervention in routine clinical practice. For PCTs, the hypotheses and study design are formulated based on information needed to make a clinical decision. The most pragmatic of PCTs simply build in randomisation at point of care and collect trial outcomes from existing electronic data sources.

All three countries recognise that experience with pragmatic trials is limited and best practices regarding design and reporting methodologies are undeveloped.

Pragmatic trials limit the use of strict eligibility criteria to maximise external validity²⁷. But the requirement to maximise external validity poses design challenges. For example, if trial

integrity is highly dependent on collective participation; informed consent may compromise the real-world nature of the trial. Pragmatic trials often employ cluster designs which require special statistical consideration. To overcome the ethical issues associated with waiver of informed consent, others may utilise prompted optional randomisation²⁸ that may result in a less precise estimate of treatment effect.

FIGURE 4: What makes a trial design pragmatic?

Commonly cited characteristics of pragmatic trials ^{29,30}	
Purpose:	To inform decision-makers
Study Design:	RCT, Cluster RT, Step Wedge, Cohort Multiple-Randomised
Study Population:	Heterogeneous (minimal eligibility criteria)
Setting:	Commonly where patients already receive their usual clinical care
Endpoints:	Important to patients, typically encountered in clinical care
Follow-up:	Aligned with standard care
Data	Existing electronic sources (e.g. EMR)
Monitoring:	Minimal
Cost	Low (median cost per patient - \$97 over 64 trials reported by Ramsberg & Platt)

The Explanatory-Pragmatic Continuum

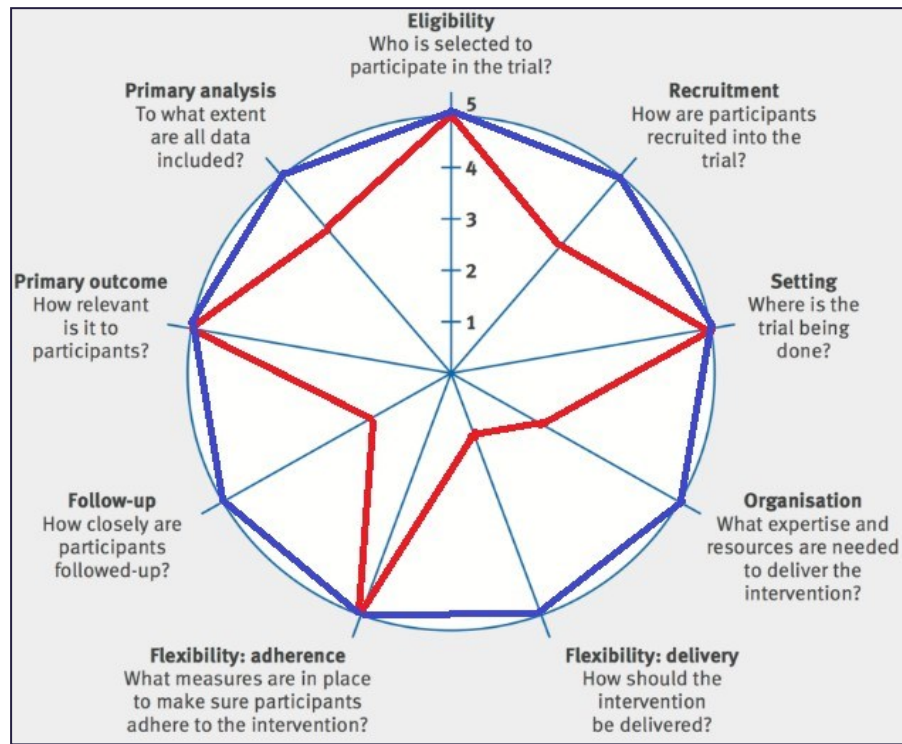
Few trials are entirely explanatory (conducted in an idealised setting) or entirely pragmatic (conducted in a usual-care setting). One tool that has been widely adopted in the UK, US and Canada is the Pragmatic-Explanatory Continuum Indicator Summary [PRECIS-2](#)³¹. PRECIS-2 is used to determine where a trial sits on the explanatory-pragmatic continuum. The tool was designed to help investigators consider the effects of their design decisions on the applicability of their results in clinical settings.



Image from the NIH Collaboratory
Introduction to Pragmatic Clinical Trials

FIGURE 5: The Preci- 2 Wheel

An example of two trials – The BLUE line shows a highly pragmatic trial, and the RED line shows a trial further along the explanatory-pragmatic continuum³².



The dearth of trialists with experience developing pragmatic trial designs is well recognised. In the US, the collective experience of designing and conducting Pragmatic Demonstration Projects in a variety of settings, is provided to researchers in the NIH Collaboratory [Living Textbook](#). PCORI also provide a [suite of standards](#).

In the UK, the Network of Hubs for Trials Methodology Research ([HTMR](#)) is a collaboration of seven centres. The Network provides a national platform for research in methodology related to the design, conduct, and analysis of trials, and has strong links to local clinical trials units that execute trial design and trial management. The MRC is also involved in the [Methodology Research Program](#) funded by the NIHR. Although not specific for pragmatic trials, [Trial Forge](#) is another initiative that aims to increase the evidence base for trial decision making and, in doing so, improve trial efficiency.

Adaptive and Bayesian Trial Design

Randomised, embedded, multifactorial adaptive platform trials such as [REMAP-CAP](#), are now being conducted in greater numbers. They have the potential to merge clinical trials and routine clinical practice to identify the optimal treatment for a disease. REMAPs have in-built implementation, both while evidence is still being generated (using response adaptive randomisation) and after results are generated by using trial processes to specify provision of treatments that have been proven to be effective³³. PCORI is working to develop designs that better integrate into a dynamic, healthcare system and are encouraging response-adaptive platform designs³⁴. The [PCORI Methodology Standards](#) provide guidance on Adaptive and Bayesian trial designs as do the MRC

Methodological Hubs with publications and guidance to support [adaptive trial design](#). Their work on multi-arm, multistage-stage platform trials ([MAMs designs](#)) utilises an intermediate outcome measure at the interim stages to reduce the length of time to complete the trial.

5 A CULTURE THAT VALUES RESEARCH

Organisations that adopt a culture that values research encourage research participation, provide opportunities for staff to acquire research skills, recognise research achievements and invest resources in research activity³⁵. However, there is acute awareness in all countries that although trials are designed to improve practice and policy, the intense pressure on healthcare organisations to deliver immediate healthcare targets is a significant barrier to embedding clinical trials. Additionally, a lack of perception of any immediate benefit brought about by research can cause health care organisations to give research a low priority. The NIH Collaboratory Stakeholder Engagement Core and the IOM have extensively surveyed the issues surrounding stakeholder engagement and both entities conclude that a successful move to a Learning Healthcare System engages health system leaders and the clinical and service delivery workforce at the outset³⁶.

5.1 ENGAGING HEALTH SYSTEM LEADERS

Remember, the purpose of the healthcare system is not to do research, but to provide good healthcare. Researchers often have a tail-wagging-the-dog problem. We assume if we think something is a good idea, the healthcare system will too. We need to remember that the mission is to improve peoples' healthcare. We need to remember that we're the tail and the healthcare system is the dog (Dr G Simon)

Larson, E, B et al. 2015, Trials without tribulations: Minimizing the burden of pragmatic research on healthcare systems. Healthcare.

According to the IOM³⁷, health system leaders are interested in research studies that support organisational performance goals; provide data to drive decision-making; enhance delivery-system reputation and national and community connections; and ultimately support the goal of high-quality, patient-centred care at a reasonable cost. As such, the results of pragmatic trials are implementable and sustainable if they align around these goals.

England has adopted 'carrot and stick' approach to ensure research is a priority in the NHS. [Research capability funding](#) encourages NHS organisations to be research active. The NIHR also publish [annual league tables](#) and [performance metrics](#) that show the extent of research activity across England and that enable research site performance to be compared.

In order to demonstrate the value proposition for clinical trials, the NIHR have funded studies to examine the link between research activity and hospital outcomes which has produced evidence that suggests that hospitals supporting high quality patient-centred research have better healthcare outcomes³⁸. One study investigated whether clinical research activity was associated with established outcome measures such as Clinical Quality Care (CQC) ratings and showed a significant correlation with better CQC ratings as well as lower Summary Hospital-level Mortality Indicator scores³⁹. This has led to a partnership between the NIHR and the Care Quality Commission (CQC), to develop new [research indicators](#) for use as part of CQC's

monitoring and inspection program. These indicators recognise the role of research in delivering quality patient care and provide an effective method for hospitals to demonstrate their research activity.

5.2 ENGAGING THE HEALTHCARE WORKFORCE

The ideal clinical trials workforce will be orders of magnitude larger than its present size, because it will include nearly all of the 90 percent of clinicians who currently are not part of the clinical trials enterprise ⁴⁰

The lack of clinician engagement has been highlighted in numerous surveys. One US survey showed only 7 percent of American adults said that their doctors have ever suggested that they participate in a clinical study⁴¹. Another survey of general practitioners⁴² found that while the majority agreed that research was important, less than a quarter felt that they should be involved personally. Time demands and lack of remuneration of clinical trial activities are cited as the two biggest barriers to participation⁴³.

To increase the evidence base for primary care practice and address the lack of engagement in research primary care, the NIHR established the [School of Primary Care Research](#). In parallel, the NIHR, through the Royal College of GPs, launched the [Research Ready® scheme](#) that upskilled and accredited over 1,000 practices in the UK. A similar scheme, Royal Pharmaceutical Society [Research Ready Accreditation](#) has been launched for community pharmacies. The [NIHR research nurse strategy](#) sets out the role that research nurses and other front-line staff play in creating a clinical research culture.

5.3 MEASURING IMPACT TO SUPPORT ENGAGEMENT

To demonstrate the value proposition to all stakeholders, mechanisms to measure impact have been introduced that place less emphasis on publication impact. The NIHR utilises [Researchfish](#) to demonstrate the benefits of investing in UK bioscience research. In the US, [Star Metrics](#) is being developed by the Federal government to enable them to document the value of its investments in research and development.



CHANGING CULTURE

- *The core role of health research in the delivery and improvement of the NHS should be more widely communicated to healthcare staff at all levels.*
- *Health research should be formally and irreversibly embedded into NHS leadership and governance processes by the following: the use of appropriate metrics and incentives; training the NHS workforce to ensure it can support health research; and ensuring that within each Trust there is an executive director with specific responsibilities to promote health research’.*

A new pathway for the regulation and governance of health research:
Academy of Medical Sciences (2011)

6 A SECURE, SKILLED WORKFORCE

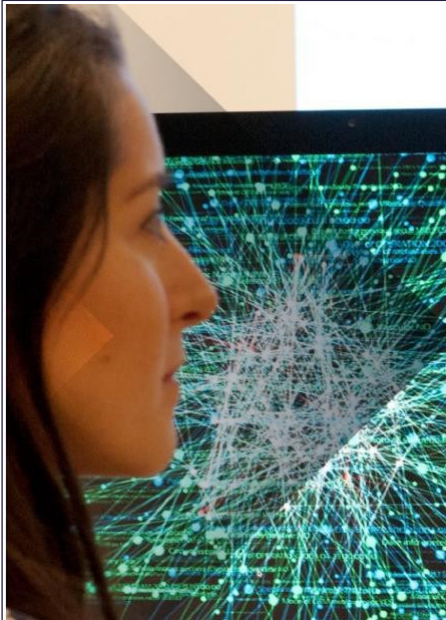
A stable workforce of skilled and experienced clinician researchers who have protected time to design and conduct research as part of (and not separate to) their clinical service is recognised as essential to effective embedding and high-quality studies.

In the US, the NIH cultivates the human capital needed to fulfil its mission by providing training grants and fellowships to graduate students and postdoctoral researchers. The [NIH MD/PhD Partnership Training Program](#) is designed to encourage the success and development of students pursuing a future as physician-scientists in basic and translational biomedical research. In England, [the NIHR Faculty](#) is the collective term for the people the NIHR support to lead and deliver health research, and to train as the next generation of health researchers. The clinical research coordinator (or research nurse) plays a key role in the research team, acting as a research champion to assist the embedding of research. In England, the network of research nurses funded by the NIHR have a professional development plan, a clear supervisory arrangement, a line of professional accountability and access to skills development activity. As part of this professional development, good clinical practice (GCP) training is provided. Creating a secure, skilled workforce that departs from the traditional model of short-term, project-by-project contract funding (often from ephemeral sources such as trust funds) enables staff to be deployed across trials within a hospital or trials network (e.g., to cover staff absences or high activity peaks). This has not only ensured that the workforce is fully utilised, it has also helped to maintain the quality of trial conduct.

The NIHR also supports the activities of the [Trial Managers’ Network](#); a community of practice and has published the [Trial Managers’ Guide](#) to provide pragmatic advice to those involved in the coordination of investigator-led trials. It also hosts the [Clinical Trials Toolkit](#) a national resource to assist non-commercial researchers navigate the trial process.

All three countries have developed competency frameworks. For example, the US AHRQ core competencies have been developed to guide the design, implementation, and evaluation of training programs for LHS researchers⁴⁴. All have identified that their current system does not adequately facilitate, incentivise, or support research by the clinical workforce^{45,46,47}. Protected research time has been recognised as one element to ensure the best health professional

researchers remain active in research. Canada's Strategy for Patient-Oriented Research⁴⁷ recognises the need of a Learning Healthcare System to train greater numbers of epidemiologists, biostatisticians, and health economists. In addition, all countries agree that progress will also depend on the development of a new cadre of 'integrated' research staff to work across disciplines in areas such as computational science, bioinformatics and molecular pathology and implementation science.



FROM ASTROPHYSICS TO A CAREER IN CLINICAL RESEARCH

The Institute of Cancer Research (ICR) in England recruits its researchers from a wide range of disciplines including people from well outside the traditional boundaries of medical research. Using vast amounts of scientific and clinical data is relatively new in cancer research – but in astrophysics, the analysis of big, complex datasets has been a longstanding challenge. Dr Carmen Rodriguez Gonzalvez was previously an astrophysics research scholar, with a strong background in the analysis of data. She has joined the ICR as a data scientist applying analytical and statistical techniques developed over decades by the astrophysics community to biological challenges.

**Making the discoveries: Our strategy to defeat cancer
2016 – 2021 (ICR/RMH)**

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Expert Reference Group: 'Embedding Clinical Trials in Healthcare'
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