

INTEGRATED CARE Primary and secondary care collaboration in clinical research

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ABSTRACT

More patients are seen in primary care than in any other part of the health system in the UK. Our NHS datasets are the envy of the world and provide us with huge opportunities to support our patients and populations. In this paper, we demonstrate the breadth of primary care research, recruitment and delivery options. We show how research can affect many different aspects of patient care and demonstrate, through the delivery and publication of game-changing research, the ability of recruitment in primary care to answer questions that are relevant to secondary care activity. Indeed, these complex and innovative study designs and their collaborative delivery across the multitude of diseases (acute and chronic) show the strength of primary care. Collaboration across boundaries, specialties and healthcare settings will provide increased opportunities for clinical research development and, most importantly, deliver the highest quality research to support our patients.

KEYWORDS: primary care, secondary care, research, Clinical Research Network

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Introduction

More patients are seen in primary care than in any other part of the health system in the UK. As of 1 January 2023, there were 62,241,689 patients registered at GP practices in England and more than 90% of consultations and direct experience of health and care happen in primary care.^{1,2} Through developing primary care research and using this connection to our patients and communities, we can build our evidence base and target preventative measures to tackle disease burden and reduce the need for patients to access secondary care services. Thus,

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it is more cost-effective for our health system and best for our patients if they are supported in the community.

The Coronavirus 2019 (COVID-19) pandemic accelerated and demonstrated the strength of UK clinical research and provided increased opportunities for people to engage with research.³ Research was prioritised and essential in the provision of care to our patients. This embedded approach exemplifies the possibility of clinical research when research is seen as everyone's business and people are enabled to support it in their clinical practice. There are huge opportunities in primary care research and these will be maximised by working together to support patients.

Background

As part of the desire to increase research activity in the UK, the National Institute of Health and Care Research (NIHR) is supporting both primary and secondary care research through the Clinical Research Network (CRN).⁴ During the pandemic, the primary care team in the NIHR CRN was asked to develop a primary care strategy that would refocus and reinvigorate activity within primary care, in a network that was traditionally focussed on secondary care clinical research activity.⁵

An explicit priority of the CRN primary care strategy is the consideration of primary care, not only as general practices and their teams, but also as a generic setting for research. This means an extension of research opportunities outside of the hospital and outside of general practice into the community, involving other independent practitioners, such as pharmacists, dentists and optometrists, as well as community staff. The comprehensive and detailed nature of GP clinical records enables rapid identification of potential participants, and the recognition that most patients with chronic disease and multiple long-term conditions are not under the care of secondary care clinicians, makes primary care an ideal setting for collaborative research.

Increasingly, however, there is a recognition that the arbitrary definitions of primary care and secondary care are increasingly becoming more blurred as vertical and horizontal integration occurs.⁶ This is also reflected in research, where the opportunities for research should be present at every stage of the patient pathway, from home to hospital. This would include several integrated care initiatives that do not fit neatly into the primary–secondary care division, such as virtual hospitals and community outreach from hospital into primary care.

The benefits for acute Trusts of taking part in research are well established. These relate to better care provided in research-active Trusts, better outcomes for staff and other important outcomes

for the health service. These are well evidenced and used as an important driver to promote research.^{7,8} Likewise, we are beginning to define in primary care several benefits for research active practices (ARAPAHO study, awaiting publication). In both sectors, these are important drivers to facilitate and promote research as being an integral part of routine clinical care.

The NIHR CRN, through its 15 constituent Local Clinical Research Networks (LCRNs), engages widely with health and social care with both secondary and primary care colleagues. In 2022–2023, 100% of acute Trusts took part in CRN research and 44% of GP practices in England recruited their patients into NIHR CRN portfolio research. Increasingly, the CRN is encouraging chief investigators and sponsors to consider collaborating with primary care colleagues, and working with primary care populations, to better demonstrate the generalisability of their study, specifically the need for research to be inclusive from an equality, diversity and inclusion (EDI) perspective, as well as placing studies in areas of maximal disease prevalence, which is not currently the case.^{9,10}

Changing practice through clinical research

In this paper, we demonstrate the breadth of primary care research and of recruitment and delivery options. We show how research can affect many different aspects of patient care and we also demonstrate, through the delivery and publication of game-changing research, the ability of recruitment in primary care to answer questions that are relevant to secondary care activity. As the boundaries between primary and secondary care become more blurred and care becomes more integrated, as promoted in the Fuller report,¹¹ the importance of offering research opportunities to patients at the most appropriate part of their care pathway is paramount.

Point-of-care testing

One aspect of a care pathway approach to research is that of point-of-care testing. This has been an area of development and focus of many care pathways for many years whether it be to guide diagnosis, monitoring or treatment. However, the lack of availability of clinical evidence has sometimes inhibited the progress and adaptation of these tests into usual clinical care, as has the need to test these initiatives in the setting where they will be deployed. One of the many examples of this is the PACE trial,¹² which investigated the use of C-reactive protein (CRP) point-of-care testing in chronic obstructive pulmonary disease (COPD) exacerbations. The trial was delivered in 86 general practices (653 randomised participants), and showed that CRP-guided prescribing of antibiotics resulted in a lower percentage of patients receiving antibiotics and, hence, improved antimicrobial stewardship.

Early diagnosis

Another key part of primary care research is that of early diagnosis, particularly in cancer. The benefits of early detection for the patient and for the health service cannot be underestimated, and improving the stage at which cancers are diagnosed is a key priority of NHS England.¹³ Primary care is receptive to novel techniques for early diagnosis.

An excellent example of this is the use of the Cytosponge to diagnose Barrett's oesophagus earlier and, hence, reduce mortality from oesophageal carcinoma. The BEST3 randomised

controlled trial,¹⁴ supported by the CRN, took place in 109 demographically diverse general practices in England and 13,514 patients with gastro-oesophageal reflux were randomly allocated to swallow the Cytosponge or to usual care for their reflux. Patients in the intervention group were asked to swallow the Cytosponge under the instruction of their practice nurse. After retrieval, the cells detected were then stained with an antibody against Trefoil Factor 3 (TFF3) to detect Barrett's oesophagus and patients subsequently underwent an endoscopy if the results were positive. The study was successfully delivered, and was acceptable to most patients, demonstrating improved detection of Barrett's oesophagus in the intervention group. This is an excellent example of a real-world study of implementation in a primary care setting.

Management of chronic disease

The past 5 years have seen the publication of some important clinical trials set in UK primary care. The results, although relevant to GPs and their teams, also have significance for secondary care specialists, because they challenge some received notions and remind us that we need to treat individuals, not just their diseases. In the OPTIMISE trial,¹⁵ Sheppard *et al.* showed that deprescribing antihypertensive medication in those over 80 years of age was not associated with a substantial change in blood pressure control. TASMINH4 provided us with evidence that self-monitoring of blood pressure during dose titration of antihypertensive medication led to significantly lower blood pressure than when using traditional clinic measurements to guide these decisions.¹⁶ Finally, in their assessment of a patient-centred care (3C) model in those with multiple health conditions, Salisbury and colleagues noted increased levels of patient satisfaction but without any significant improvement in the primary outcome, which was quality of life.¹⁷

Of course, these examples represent a very small proportion of the high-quality research originating in primary care every year, but they serve to illustrate the relevance of this work across disciplines and remind us of the unique value of the setting to healthcare researchers.

COVID-19 pandemic learning

The COVID-19 pandemic recently demonstrated the importance of clinical research in the design of new drugs and therapeutic interventions as well as the use of repurposed drugs, such as dexamethasone in the RECOVERY study.¹⁸ The development of vaccines for COVID-19 and their deployment in the population is testimony to the strength of UK clinical research.

As we emerge from the pandemic, there is widespread recognition that we need to further develop the research capability of the UK as well as increasing the ability of the UK to deliver commercial research and speed, as noted in the O'Shaughnessy report.^{19,20} This cross-sector approach to stepping up clinical research must, by definition, involve both primary and secondary care as well as the interface between them.

Data-driven research

The NHS health record is the most enviable health dataset in the world. There are several significant primary care research datasets, such as Clinical Practice Research Datalink (CPRD) and the Royal College of General Practitioners Research and Surveillance Centre

(RCGP RSC). These datasets are used in many ways to support and facilitate clinical research, and have recently been reviewed and supported by Government policy post pandemic.^{21,22}

The DaRe2THINK trial is using a variety of routinely collected data in primary and secondary care, including CPRD (one in four general practices), Hospital Episode Statistics and the Office for National Statistics.²³ This data framework, 'Dare2', allows a large number of eligible patients to be prescreened and increases the opportunity for potential participants, including those who have not previously taken part in research, to engage. This approach embeds a randomised control trial in the primary care setting and investigates whether earlier use of direct oral anticoagulants can prevent thromboembolic events and cognitive decline in patients with prior or current atrial fibrillation. Participants can be remotely screened, consented and followed up, allowing greater numbers to participate.

Early in the pandemic the RCGP RSC (one of Europe's oldest sentinel systems, established in 1957) saw significant growth in its membership (now over 2,000 member practices) as a result of both its COVID-19 surveillance work and its role in supporting the Platform Randomised trial of treatments in the Community for epidemic and Pandemic influenza (PRINCIPLE) trial.^{24,25} The PRINCIPLE trial was the first response-adaptive, platform trial ever done in primary care, using Bayesian approaches for faster time to result, vital in its search to identify an early effective treatment for COVID-19 from repurposed potential candidates.

It was the first UK-wide truly 'democratic' trial of medicines where people were able to join the study irrespective of where they lived and where they received their health care. It randomised 11,768 participants, testing seven different repurposed medications and reported swiftly to ensure that any changes in clinical care that were necessary would be initiated at speed. The trial findings, that azithromycin and doxycycline did not work for COVID-19, made a considerable contribution to global antimicrobial stewardship,^{26,27} and inhaled budesonide (a cheap, safe, inhaled steroid used for asthma) treatment helped people recover faster and had a high probability of reducing the need for hospital care.²⁸

Innovative trial design

Whereas the PRINCIPLE study investigated the clinical effectiveness of repurposed drugs for COVID-19 in the community, it became clear in mid-2021 that there was a need for novel agents to be tested in a large clinical and cost-effectiveness trial in primary care. Therefore, the Platform Adaptive trial of Novel antiVirals for early treatment of COVID-19 in the Community (PANORAMIC) RCT was funded by the NIHR and led by primary care colleagues from the University of Oxford.

Building on the learning from the PRINCIPLE study, the PANORAMIC study of COVID-19 was designed to randomise symptomatic older patients, or younger patients with multiple health conditions, within 5 days of the onset of their symptoms. The study started at the height of the omicron wave of COVID-19 and the first drug studied was molnupiravir. As with PRINCIPLE, the study was delivered in the community using decentralised methods and courier delivery of the drug to the patient's house. Eligible participants were identified by their GP practice in a hub-and-spoke model allowing maximum engagement with the surrounding population through identification in the linked spoke practices and onward referral for research delivery in the hub practice.

Patients could also self-refer, following receipt of a positive test text from NHS Digital, or were signposted to the PANORAMIC trial website (www.panoramictrial.org). Recruitment was spectacularly successful, despite the rigours of the pandemic, and over 26,000 participants were randomised. The results,²⁹ that Molnupiravir did not reduce the risk of hospitalisation or death with COVID-19 in the community, but produced a quicker recovery, have been used around the world to inform treatment decisions. The on-going PANORAMIC study is currently the largest primary care-based randomised trial of treatment for COVID-19 in the world.

Vaccine research

The need to deliver safe and effective COVID-19 vaccines in timescales previously unheard of, further demonstrated the potential benefits of collaboration between sites and settings, and between primary and secondary care. Mass vaccination clinics and the infrastructure to support large-scale recruitment and follow-up brought together individuals and teams from different organisations and forged relationships that continue to bear fruit in the post-pandemic era. In the phase III trial ENSEMBLE 2,³⁰ secondary care research teams, vaccinologists and two primary care GP surgeries delivered recruitment 25% over target. This study demonstrated, among the many important lessons we have learned in recent years as a research community, the need to move away from isolated silo working and share skills that will allow us to deliver the latest complex commercial trials competitively on a global stage.

Discussion

To achieve the vision outlined in the *Future of UK Clinical Research (2022)*,¹⁹ we must work collaboratively together across settings and specialties, including early engagement with patients and primary care. This should be supported by innovative trial design and effective use of data, to support our patients and populations and increase access and opportunities for people to get involved in health and care research.

Our vision is to create a research culture across the NHS and all health and care settings, where all staff feel empowered and supported to participate in clinical research delivery.¹⁹

The UK government is committed to the development of clinical research in the UK. The recently commissioned O'Shaughnessy review highlights opportunities to build on the work of the NIHR and partners, to address challenges in the system.²⁰ This includes increased opportunities for working with industry to increase commercial research. During the COVID-19 pandemic, the UK demonstrated our ability to deliver clinical research and our strength on the world stage. Our NHS datasets are the envy of the world and provide us with huge opportunities to support our patients and populations.

Decentralised trials and new innovative trial design will enable more patients, particularly those in underserved groups, to take part in research and, therefore, increase research inclusion. Early engagement with primary care and co-design with patients and communities are essential to support this. Alongside this, we must develop our workforce and create more opportunities for GPs and primary care staff to deliver, design and engage with research.

ICs and the UK Government's commitment to the development of clinical research offer us increased opportunities to collaborate

across boundaries, specialties and settings. Together, we can deliver the highest quality research to support our patients. ■

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